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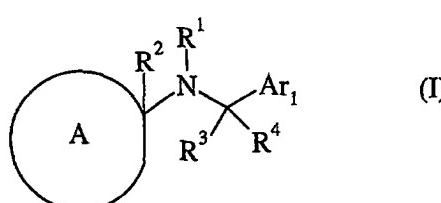
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[Continued on next page]

(54) Title: 3-AMINOPIPERIDINES AND 3-AMINOQUINUCLIDINES AS INHIBITORS OF MONOAMINE UPTAKE



(57) Abstract: The present invention provides compounds of formula (I) and pharmaceutically acceptable salts thereof, which are useful for the inhibition of the uptake of one or more physiologically active monoamines (serotonin, norepinephrine, and dopamine).

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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**3-AMINOPIPERIDINES AND 3-AMINOQUINUCLIDINES  
AS INHIBITORS OF MONOAMINE UPTAKE**

The present invention is directed to compounds which inhibit the uptake of one or more physiologically active monoamines selected from serotonin (also called 5-hydroxytryptamine or 5-HT), norepinephrine (also called noradrenaline) and dopamine. There is a large body of scientific evidence pointing to the physiological role of these monoamines as neurotransmitters. Consequently, compounds which are capable of inhibiting the uptake of one or more of these monoamines find utility in the treatment of disorders of the central and/or peripheral nervous system.

It is known that the 3-aryloxy-3-substituted-1-aminopropane class of compounds have demonstrated particular diversity in their ability to inhibit the uptake of monoamines. Fluoxetine (N-methyl 3-((4-trifluoromethylphenyl)oxy)-3-phenyl-1-aminopropane hydrochloride), for example, is a selective serotonin uptake inhibitor that has found great market acceptance in the treatment of depression and has also been approved for the treatment of a number of other disorders. Atomoxetine ((-)-N-methyl 3-((2-methylphenyl)oxy)-3-phenyl-1-aminopropane hydrochloride), is a selective norepinephrine uptake inhibitor that is approved for the treatment of attention deficit/hyperactivity disorder. Duloxetine ((+)-N-methyl 3-(1-naphthalenyl)oxy)-3-(2-thienyl)-1-aminopropane hydrochloride), is a dual serotonin and norepinephrine uptake inhibitor that is in clinical development for the treatment of depression and stress urinary incontinence.

WO 91/09844 discloses 2-aryl-3-(N-arylmethylamino)piperidines as substance P antagonists.

WO93/01170 discloses another generic class of 3-amino-aza-cycloalkanes/alkenes as substance P antagonists.

WO93/15073 describes azabicyclic compounds as calcium channel antagonists.

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WO94/13291 discloses a generic class of cyclic secondary amine derivatives as calcium channel antagonists.

- 5 WO02/24649 discloses a generic class of substituted amino-aza-cycloalkanes as inhibitors of the plasmodium falciparum protease plasmepsin II or related aspartic proteases.

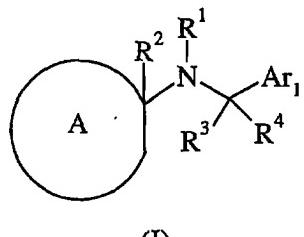
- 10 WO2004/016608 describes certain quinuclidine derivatives that are modulators of the nicotinic and/or of the monoamine receptors.

It would be advantageous to provide further compounds which are capable of inhibiting the uptake of one or more monoamines selected from serotonin, norepinephrine and dopamine. Preferably, such compounds would exhibit one or more of the following

- 15 characteristics when compared with known monoamine uptake inhibitors – (i) improved potency in their inhibition of one or more of these monoamines, (ii) improved selectivity in their inhibition of one or more of these monoamines, (iii) improved bioavailability, (iv) minimal interaction with metabolic enzymes such as CYP2D6 and (v) improved acid stability.

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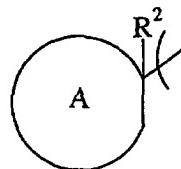
Accordingly, the present invention provides a compound of formula (I)



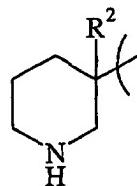
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wherein

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is a group of formula (a) or (b)

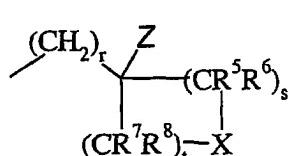


(a)

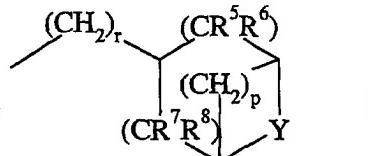


(b)

- $R^1$  is  $C_1-C_6$  alkyl (optionally substituted with 1, 2 or 3 halo substituents and/or with 1 substituent selected from  $-S-(C_1-C_3$  alkyl),  $-O-(C_1-C_3$  alkyl) (optionally substituted with 1, 5 2 or 3 F atoms),  $-O-(C_3-C_6$  cycloalkyl),  $-SO_2-(C_1-C_3$  alkyl),  $-CN$ ,  $-COO-(C_1-C_2$  alkyl) and  $-OH$ );  $C_2-C_6$  alkenyl;  $-(CH_2)_q-Ar_2$ ; or a group of formula (i) or (ii)



(i)



(ii)

- $R^2$ ,  $R^3$  and  $R^4$  are each independently selected from hydrogen or  $C_1-C_2$  alkyl;
- 10  $R^5$ ,  $R^6$ ,  $R^7$  and  $R^8$  are at each occurrence independently selected from hydrogen or  $C_1-C_2$  alkyl;
- $-X-$  is a bond,  $-CH_2-$ ,  $-CH=CH-$ ,  $-O-$ ,  $-S-$ , or  $-SO_2-$ ;
- $-Y-$  is a bond,  $-CH_2-$  or  $-O-$ ;
- $-Z$  is hydrogen,  $-OH$  or  $-O-(C_1-C_3$  alkyl);
- 15  $p$  is 0, 1 or 2;
- $q$  is 0, 1 or 2;
- $r$  is 0 or 1;
- $s$  is 0, 1, 2 or 3;
- $t$  is 0, 1, 2, 3 or 4;
- 20  $Ar_1$  is selected from:

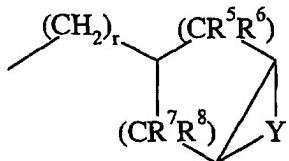
- (i) a phenyl group or a 5- or 6-membered monocyclic heteroaromatic group each of which is optionally substituted with 1, 2, 3, 4 or 5 substituents (depending on the number of available substitution positions) each independently selected from halo, cyano, C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C<sub>1</sub>-C<sub>4</sub> alkyl)  
5 (optionally substituted with 1, 2 or 3 F atoms) and -S-(C<sub>1</sub>-C<sub>4</sub> alkyl) (optionally substituted with 1, 2 or 3 F atoms) and/or with 1 substituent selected from pyridinyl, pyrazolyl, phenyl (optionally substituted with 1, 2 or 3 halo substituents), benzyl (optionally substituted with 1, 2 or 3 halo substituents) and phenoxy (optionally substituted with 1, 2 or 3 halo substituents) with the proviso that only C<sub>1</sub>-C<sub>4</sub>alkyl  
10 may be a substituent for the H of any -NH- moiety present within a 5- or 6-membered monocyclic heteroaromatic group; or
  - (ii) a naphthyl group or an 8-, 9- or 10-membered bicyclic heteroaromatic group each of which is optionally substituted with 1, 2, 3, 4, 5 or 6 substituents (depending on the number of available substitution positions) each independently selected from halo, cyano, C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C<sub>1</sub>-C<sub>4</sub> alkyl)  
15 (optionally substituted with 1, 2 or 3 F atoms) and -S-(C<sub>1</sub>-C<sub>4</sub> alkyl) (optionally substituted with 1, 2 or 3 F atoms) with the proviso that only C<sub>1</sub>-C<sub>4</sub>alkyl may be a substituent for the H of any -NH- moiety present within an 8-, 9- or 10-membered bicyclic heteroaromatic group; and
- 20 Ar<sub>2</sub> is selected from
- (i) a phenyl group or a 5- or 6-membered monocyclic heteroaromatic group each of which is optionally substituted with 1, 2, 3, 4 or 5 substituents (depending on the number of available substitution positions) each independently selected from halo, cyano, C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C<sub>1</sub>-C<sub>4</sub> alkyl)  
25 (optionally substituted with 1, 2 or 3 F atoms) and -S-(C<sub>1</sub>-C<sub>4</sub> alkyl) (optionally substituted with 1, 2 or 3 F atoms) with the proviso that only C<sub>1</sub>-C<sub>4</sub>alkyl may be a substituent for the H of any -NH- moiety present within a 5- or 6-membered monocyclic heteroaromatic group; or
  - (ii) a naphthyl group or an 8-, 9- or 10-membered bicyclic heteroaromatic group each of which is optionally substituted with 1, 2, 3, 4, 5 or 6 substituents (depending on the

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- number of available substitution positions) each independently selected from halo, cyano, C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C<sub>1</sub>-C<sub>4</sub> alkyl) (optionally substituted with 1, 2 or 3 F atoms) and -S-(C<sub>1</sub>-C<sub>4</sub> alkyl) (optionally substituted with 1, 2 or 3 F atoms) with the proviso that only C<sub>1</sub>-C<sub>4</sub>alkyl may be a substituent for the H of any -NH- moiety present within an 8-, 9- or 10-membered bicyclic heteroaromatic group;
- 5 or a pharmaceutically acceptable salt thereof; provided that
- (a) the cyclic portion of the group of formula (i) must contain at least three carbon atoms and not more than seven ring atoms;
- 10 (b) when -X- is -CH=CH-, then the cyclic portion of the group of formula (i) must contain at least five carbon atoms; and
- (c) when -Z is -OH or -O-(C<sub>1</sub>-C<sub>3</sub> alkyl), then -X- is -CH<sub>2</sub>-; and
- (d) when -Y- is -O- then p cannot be 0.
- 15 For the avoidance of doubt relating to the term "and/or", when R<sup>1</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl, it is substituted with 0, 1, 2 or 3 halo substituents and with 0 or 1 substituent selected from -S-(C<sub>1</sub>-C<sub>3</sub> alkyl), -O-(C<sub>1</sub>-C<sub>3</sub> alkyl) (optionally substituted with 1, 2 or 3 F atoms), -O-(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>3</sub> alkyl), -CN, -COO-(C<sub>1</sub>-C<sub>2</sub> alkyl) and -OH.
- 20 Similarly, when Ar<sub>1</sub> is a phenyl group or a 5- or 6-membered monocyclic heteroaromatic group, each is substituted with 0, 1, 2, 3, 4 or 5 substituents (depending on the number of available substitution positions) each independently selected from halo, cyano, C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C<sub>1</sub>-C<sub>4</sub> alkyl) (optionally substituted with 1, 2 or 3 F atoms) and -S-(C<sub>1</sub>-C<sub>4</sub> alkyl) (optionally substituted with 1, 2 or 3 F atoms) and with 0 or 1 substituent selected from pyridinyl, pyrazolyl, phenyl (optionally substituted with 1, 2 or 3 halo substituents), benzyl (optionally substituted with 1, 2 or 3 halo substituents) and phenoxy (optionally substituted with 1, 2 or 3 halo substituents) with the proviso that only C<sub>1</sub>-C<sub>4</sub>alkyl may be a substituent for the H of any -NH- moiety present within a 5- or 6-membered monocyclic heteroaromatic group.
- 25

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For the avoidance of doubt, when  $p = 0$ , the group of formula (ii) becomes



In the present specification the term "C<sub>1</sub>-C<sub>6</sub> alkyl" means a monovalent unsubstituted

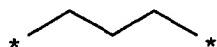
- 5 saturated straight-chain or branched-chain hydrocarbon radical having from 1 to 6 carbon atoms.

In the present specification the term "C<sub>2</sub>-C<sub>6</sub> alkenyl" means a monovalent unsubstituted unsaturated straight-chain or branched-chain hydrocarbon radical having from 2 to 6

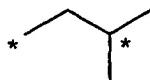
- 10 carbon atoms and containing at least one carbon-carbon double bond.

In the present specification the term "C<sub>3</sub>-C<sub>6</sub> cycloalkyl" means a monovalent unsubstituted saturated cyclic hydrocarbon radical having from 3 to 6 carbon atoms.

- 15 In the present specification the term "C<sub>1</sub>-C<sub>6</sub> alkylene" means a divalent unsubstituted saturated straight-chain or branched-chain hydrocarbon radical having from 1 to 6 carbon atoms. This term is not limited to divalent radicals wherein the radical carbon atoms are located at the termini of the hydrocarbon chain, for example



- 20 but also include divalent radicals wherein the radical carbon atoms are located within the hydrocarbon chain, for example



In the present specification the term "halo" or "halogen" means F, Cl, Br or I.

In the present specification the term “C<sub>1</sub>-C<sub>4</sub> difluoroalkyl” means a monovalent unsubstituted saturated straight-chain or branched-chain hydrocarbon radical having from 1 to 4 carbon atoms wherein two hydrogen atoms are substituted with two fluoro atoms. Preferably the two fluoro atoms are attached to the same carbon atom.

5

In the present specification the term “C<sub>1</sub>-C<sub>4</sub> trifluoroalkyl” means a monovalent unsubstituted saturated straight-chain or branched-chain hydrocarbon radical having from 1 to 4 carbon atoms wherein three hydrogen atoms are substituted with three fluoro atoms. Preferably the three fluoro atoms are attached to the same carbon atom.

10

In the present specification the term “benzyl” means a monovalent unsubstituted phenyl radical linked to the point of substitution by a -CH<sub>2</sub>- group.

15

In the present specification the term “phenoxy” means a monovalent unsubstituted phenyl radical linked to the point of substitution by an O atom.

20

In the present specification the term “5- or 6-membered monocyclic heteroaromatic group” means a monocyclic aromatic group with a total of 5 or 6 atoms in the ring wherein from 1 to 4 of those atoms are each independently selected from N, O and S.

25

Preferred groups have 1 or 2 atoms in the ring which are each independently selected from N, O and S. Examples of 5-membered monocyclic heteroaromatic groups include pyrrolyl (also called azolyl), furanyl, thienyl, pyrazolyl (also called 1H-pyrazolyl and 1,2-diazolyl), imidazolyl, oxazolyl (also called 1,3-oxazolyl), isoxazolyl (also called 1,2-oxazolyl), thiazolyl (also called 1,3-thiazolyl), isothiazolyl (also called 1,2-thiazolyl), triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, oxatriazolyl and thiatriazolyl. Examples of 6-membered monocyclic heteroaromatic groups include pyridinyl, pyrimidyl, pyrazinyl, pyridazinyl and triazinyl.

“Pyrrolyl” as used herein includes pyrrol-1-yl, pyrrol-2-yl and pyrrol-3-yl.

30

“Furanyl” (also called “furyl”) as used herein includes furan-2-yl and furan-3-yl (also called 2-furyl and 3-furyl). Furan-2-yl is preferred.

“Thienyl” (also called “thiophenyl”) as used herein includes thien-2-yl and thien-3-yl (also called 2-thiophenyl and 3-thiophenyl).

“Pyrazolyl” as used herein includes pyrazol-1-yl, pyrazol-3-yl, pyrazol-4-yl and pyrazol-5-yl (also called 1-pyrazole, 3-pyrazole, 4-pyrazole and 5-pyrazole). Pyrazol-1-yl is  
5 preferred.

“Imidazolyl” as used herein includes imidazol-1-yl, imidazol-2-yl, imidazol-4-yl and imidazol-5-yl.

“Oxazolyl” as used herein includes oxazol-2-yl, oxazol-4-yl and oxazol-5-yl.

“Isooxazolyl” as used herein includes isoaxazol-3-yl, isoaxazol-4-yl, and isoaxazol-5-yl.

10 “Thiazolyl” as used herein includes thiazol-2-yl, thiazol-4-yl and thiazol-5-yl (also called 2-thiazolyl, 4-thiazolyl and 5-thiazolyl).

“Isothiazolyl” as used herein includes isothiazol-3-yl, isothiazol-4-yl, and isothiazol-5-yl.

“Triazolyl” as used herein includes 1,2,3-triazol-1-yl, 1,2,3-triazol-4-yl, 1,2,3-triazol-5-yl, 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl and 1,2,4-triazol-5-yl.

15 “Oxadiazolyl” as used herein includes 1,2,3-oxadiazol-4-yl, 1,2,3-oxadiazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,2,5-oxadiazol-3-yl and 1,3,4-oxadiazol-2-yl.

“Thiadiazolyl” as used herein includes 1,2,3-thiadiazol-4-yl, 1,2,3-thiadiazol-5-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 1,2,5-thiadiazol-3-yl (also called furazan-3-yl) and 1,3,4-thiadiazol-2-yl.

20 “Tetrazolyl” as used herein includes tetrazol-1-yl and tetrazol-5-yl.

“Oxatriazolyl” as used herein includes 1,2,3,4-oxatriazol-5-yl and 1,2,3,5-oxatriazol-4-yl.

“Thiatriazolyl” as used herein includes 1,2,3,4-thiatriazol-5-yl and 1,2,3,5-thiatriazol-4-yl.

25 “Pyridinyl” (also called “pyridyl”) as used herein includes pyridin-2-yl, pyridin-3-yl and pyridin-4-yl (also called 2-pyridyl, 3-pyridyl and 4-pyridyl).

“Pyrimidyl” as used herein includes pyrimid-2-yl, pyrimid-4-yl, pyrimid-5-yl and pyrimid-6-yl.

“Pyridazinyl” as used herein includes pyridazin-3-yl and pyridazin-4-yl.

“Pyrazinyl” as used herein includes pyrazin-2-yl and pyrazin-3-yl.

30 “Triazinyl” as used herein includes 1,3,5-triazin-2-yl, 1,2,4-triazin-3-yl, 1,2,4-triazin-5-yl, 1,2,4-triazin-6-yl, 1,2,3-triazin-4-yl and 1,2,3-triazin-5-yl.

- In the present specification the term “8-, 9- or 10-membered bicyclic heteroaromatic group” means a fused bicyclic aromatic group with a total of 8, 9 or 10 atoms in the ring system wherein from 1 to 4 of those atoms are each independently selected from N, O and S. Preferred groups have from 1 to 3 atoms in the ring system which are each independently selected from N, O and S. Suitable 8-membered bicyclic heteroaromatic groups include imidazo[2,1-b][1,3]thiazolyl, thieno[3,2-b]thienyl, thieno[2,3-d][1,3]thiazolyl and thieno[2,3-d]imidazolyl. Suitable 9-membered bicyclic heteroaromatic groups include indolyl, isoindolyl, benzofuranyl (also called benzo[b]furanyl), isobenzofuranyl (also called benzo[c]furanyl), benzothienyl (also called benzo[b]thienyl), isobenzothienyl (also called benzo[c]thienyl), indazolyl, benzimidazolyl, 1,3-benzoxazolyl, 1,2-benzisoxazolyl, 2,1-benzisoxazolyl, 1,3-benzothiazolyl, 1,2-benzoisothiazolyl, 2,1-benzoisothiazolyl, benzotriazolyl, 1,2,3-benzoxadiazolyl, 2,1,3-benzoxadiazolyl, 1,2,3-benzothiadiazolyl, 2,1,3-benzothiadiazolyl, thienopyridinyl, purinyl and imidazo[1,2-a]pyridine. Suitable 10-membered bicyclic heteroaromatic groups include quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, quinoxalinyl, 1,5-naphthyridyl, 1,6-naphthyridyl, 1,7-naphthyridyl and 1,8-naphthyridyl.
- “Imidazo[2,1-b][1,3]thiazolyl” as used herein includes imidazo[2,1-b][1,3]thiazol-2-yl, imidazo[2,1-b][1,3]thiazol-3-yl, imidazo[2,1-b][1,3]thiazol-5-yl and imidazo[2,1-b][1,3]thiazol-6-yl.
- “Thieno[3,2-b]thienyl” as used herein includes thieno[3,2-b]thien-2-yl, thieno[3,2-b]thien-3-yl, thieno[3,2-b]thien-5-yl and thieno[3,2-b]thien-6-yl.
- “Thieno[2,3-d][1,3]thiazolyl” as used herein includes thieno[2,3-d][1,3]thiazol-2-yl, thieno[2,3-d][1,3]thiazol-5-yl and thieno[2,3-d][1,3]thiazol-6-yl.
- “Thieno[2,3-d]imidazolyl” as used herein includes thieno[2,3-d]imidazol-2-yl, thieno[2,3-d]imidazol-4-yl and thieno[2,3-d]imidazol-5-yl.
- “Indolyl” as used herein includes indol-1-yl, indol-2-yl, indol-3-yl, indol-4-yl, indol-5-yl, indol-6-yl and indol-7-yl.

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- “Isoindolyl” as used herein includes isoindol-1-yl, isoindol-2-yl, isoindol-3-yl, isoindol-4-yl, isoindol-5-yl, isoindol-6-yl and isoindol-7-yl.
- “Benzofuranyl” as used herein includes benzofuran-2-yl, benzofuran-3-yl, benzofuran-4-yl, benzofuran-5-yl, benzofuran-6-yl and benzofuran-7-yl.
- 5 “Isobenzofuranyl” as used herein includes isobenzofuran-1-yl, isobenzofuran-3-yl, isobenzofuran-4-yl, isobenzofuran-5-yl, isobenzofuran-6-yl and isobenzofuran-7-yl.
- “Benzothienyl” (also called “benzothiophenyl”) as used herein includes benzothien-2-yl, benzothien-3-yl, benzothien-4-yl, benzothien-5-yl, benzothien-6-yl and benzothien-7-yl (also called 2-benzo[b]thiophenyl, 3-benzo[b]thiophenyl, 4-benzo[b]thiophenyl, 5-
- 10 10 benzo[b]thiophenyl, 6-benzo[b]thiophenyl and 7-benzo[b]thiophenyl).
- “Isobenzothienyl” as used herein includes isobenzothien-1-yl, isobenzothien-3-yl, isobenzothien-4-yl, isobenzothien-5-yl, isobenzothien-6-yl and isobenzothien-7-yl.
- “Indazolyl” as used herein includes indazol-1-yl, indazol-3-yl, indazol-4-yl, indazol-5-yl, indazol-6-yl and indazol-7-yl.
- 15 “Benzimidazolyl” as used herein includes benzimidazol-1-yl, benzimidazol-2-yl, benzimidazol-4-yl, benzimidazol-5-yl, benzimidazol-6-yl and benzimidazol-7-yl.
- “1,3-Benzoxazolyl” as used herein includes 1,3-benzoxazol-2-yl, 1,3-benzoxazol-4-yl, 1,3-benzoxazol-5-yl, 1,3-benzoxazol-6-yl and 1,3-benzoxazol-7-yl.
- 20 “1,2-Benzisoxazolyl” as used herein includes 1,2-benzisoxazol-3-yl, 1,2-benzisoxazol-4-yl, 1,2-benzisoxazol-5-yl, 1,2-benzisoxazol-6-yl and 1,2-benzisoxazol-7-yl.
- “2,1-Benzisoxazolyl” as used herein includes 2,1-benzisoxazol-3-yl, 2,1-benzisoxazol-4-yl, 2,1-benzisoxazol-5-yl, 2,1-benzisoxazol-6-yl and 2,1-benzisoxazol-7-yl.
- 25 “1,3-Benzothiazolyl” as used herein includes 1,3-benzothiazol-2-yl, 1,3-benzothiazol-4-yl, 1,3-benzothiazol-5-yl, 1,3-benzothiazol-6-yl and 1,3-benzothiazol-7-yl.
- “1,2-Benzoisothiazolyl” as used herein includes 1,2-benzoisothiazol-3-yl, 1,2-benzoisothiazol-4-yl, 1,2-benzoisothiazol-5-yl, 1,2-benzoisothiazol-6-yl and 1,2-benzoisothiazol-7-yl.
- 30 “2,1-Benzoisothiazolyl” as used herein includes 2,1-benzoisothiazol-3-yl, 2,1-benzoisothiazol-4-yl, 2,1-benzoisothiazol-5-yl, 2,1-benzoisothiazol-6-yl and 2,1-benzoisothiazol-7-yl.

“Benzotriazolyl” as used herein includes benzotriazol-1-yl, benzotriazol-4-yl, benzotriazol-5-yl, benzotriazol-6-yl and benzotriazol-7-yl.

“1,2,3-Benzoxadiazolyl” as used herein includes 1,2,3-benzoxadiazol-4-yl, 1,2,3-benzoxadiazol-5-yl, 1,2,3-benzoxadiazol-6-yl and 1,2,3-benzoxadiazol-7-yl.

5 “2,1,3-Benzoxadiazolyl” as used herein includes 2,1,3-benzoxadiazol-4-yl, 2,1,3-benzoxadiazol-5-yl, 2,1,3-benzoxadiazol-6-yl and 2,1,3-benzoxadiazol-7-yl.

“1,2,3-Benzothiadiazolyl” as used herein includes 1,2,3-benzothiadiazol-4-yl, 1,2,3-benzothiadiazol-5-yl, 1,2,3-benzothiadiazol-6-yl and 1,2,3-benzothiadiazol-7-yl.

10 “2,1,3-Benzothiadiazolyl” as used herein includes 2,1,3-benzothiadiazol-4-yl, 2,1,3-benzothiadiazol-5-yl, 2,1,3-benzothiadiazol-6-yl and 2,1,3-benzothiadiazol-7-yl.

“Thienopyridinyl” as used herein includes thieno[2,3-b]pyridinyl, thieno[2,3-c]pyridinyl, thieno[3,2-c]pyridinyl and thieno[3,2-b]pyridinyl.

“Purinyl” as used herein includes purin-2-yl, purin-6-yl, purin-7-yl and purin-8-yl.

15 “Imidazo[1,2-a]pyridinyl” as used herein includes imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyridin-3-yl, imidazo[1,2-a]pyridin-4-yl, imidazo[1,2-a]pyridin-5-yl, imidazo[1,2-a]pyridin-6-yl and imidazo[1,2-a]pyridin-7-yl.

“Quinolinyl” as used herein includes quinolin-2-yl, quinolin-3-yl, quinolin-4-yl, quinolin-5-yl, quinolin-6-yl, quinolin-7-yl and quinolin-8-yl.

20 “Isoquinolinyl” as used herein includes isoquinolin-1-yl, isoquinolin-3-yl, isoquinolin-4-yl, isoquinolin-5-yl, isoquinolin-6-yl, isoquinolin-7-yl and isoquinolin-8-yl.

“Cinnolinyl” as used herein includes cinnolin-3-yl, cinnolin-4-yl, cinnolin-5-yl, cinnolin-6-yl, cinnolin-7-yl and cinnolin-8-yl.

“Quinazolinyl” as used herein includes quinazolin-2-yl, quinazolin-4-yl, quinazolin-5-yl, quinazolin-6-yl, quinazolin-7-yl and quinazolin-8-yl.

25 “1,4-Naphthyridyl” as used herein includes 1,4-naphthyrid-2-yl, 1,4-naphthyrid-3-yl, 1,4-naphthyrid-5-yl, 1,4-naphthyrid-6-yl, 1,4-naphthyrid-7-yl and 1,4-naphthyrid-8-yl.

“1,5-Naphthyridyl” as used herein includes 1,5-naphthyrid-2-yl, 1,5-naphthyrid-3-yl, 1,5-naphthyrid-4-yl, 1,5-naphthyrid-6-yl, 1,5-naphthyrid-7-yl and 1,5-naphthyrid-8-yl.

30 “1,6-Naphthyridyl” as used herein includes 1,6-naphthyrid-2-yl, 1,6-naphthyrid-3-yl, 1,6-naphthyrid-4-yl, 1,6-naphthyrid-5-yl, 1,6-naphthyrid-7-yl and 1,6-naphthyrid-8-yl.

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"1,7-Naphthyridyl" as used herein includes 1,7-naphthyrid-2-yl, 1,7-naphthyrid-3-yl, 1,7-naphthyrid-4-yl, 1,7-naphthyrid-5-yl, 1,7-naphthyrid-6-yl and 1,7-naphthyrid-8-yl.

"1,8-Naphthyridyl" as used herein includes 1,8-naphthyrid-2-yl, 1,8-naphthyrid-3-yl, 1,8-naphthyrid-4-yl, 1,8-naphthyrid-5-yl, 1,8-naphthyrid-6-yl and 1,8-naphthyrid-7-yl.

5

In the present specification the term "naphthyl" includes 1-naphthyl, and 2-naphthyl. 1-naphthyl is preferred.

In the above definitions, similar terms specifying different numbers of C atoms take an  
10 analogous meaning. For example the terms "C<sub>1</sub>-C<sub>4</sub> alkyl" and "C<sub>1</sub>-C<sub>3</sub> alkyl" mean a monovalent unsubstituted saturated straight-chain or branched-chain hydrocarbon radical having from 1 to 4 and 1 to 3 carbon atoms respectively. The term "C<sub>1</sub>-C<sub>4</sub> alkyl" includes methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and tert-butyl. The term "C<sub>1</sub>-C<sub>3</sub> alkyl" includes methyl, ethyl, n-propyl and iso-propyl.

15

It will be appreciated that when s is 2 or 3, then each R<sup>5</sup> and/or each R<sup>6</sup> can be different. In the same way when t is 2 or 3, then each R<sup>7</sup> and/or each R<sup>8</sup> can be different.

In a preferred embodiment of the present invention, Ar<sub>1</sub> is phenyl, pyridyl, thiazolyl,  
20 benzothiophenyl or naphthyl; wherein said phenyl, pyridyl or thiazolyl group may be substituted with 1, 2 or 3 substituents each independently selected from halo, cyano, C<sub>1</sub>-C<sub>4</sub> alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C<sub>1</sub>-C<sub>4</sub> alkyl) (optionally substituted with 1, 2 or 3 F atoms) and -S-(C<sub>1</sub>-C<sub>4</sub> alkyl) (optionally substituted with 1, 2 or 3 F atoms) and/or with 1 substituent selected from pyridyl, pyrazole, phenyl  
25 (optionally substituted with 1, 2 or 3 halo substituents), benzyl and phenoxy (optionally substituted with 1, 2 or 3 halo substituents); and wherein said benzothiophenyl or naphthyl group may be optionally substituted with 1, 2 or 3 substituents each independently selected from halo, cyano, C<sub>1</sub>-C<sub>4</sub> alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C<sub>1</sub>-C<sub>4</sub> alkyl) (optionally substituted with 1, 2 or 3 F atoms), and -S-(C<sub>1</sub>-C<sub>4</sub> alkyl) (optionally substituted with 1, 2 or 3 F atoms); and  
30 Ar<sub>2</sub> is naphthyl, pyridyl, thiazolyl, furyl, thiophenyl, benzothiophenyl, or phenyl, wherein

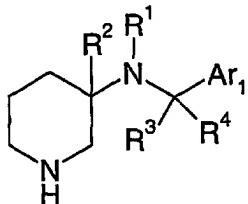
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said naphthyl, pyridyl, thiazolyl, furyl, thiophenyl, benzothiophenyl, or phenyl may be substituted with 1, 2 or 3 substituents each independently selected from halo, C<sub>1</sub>-C<sub>4</sub> alkyl (optionally substituted with 1, 2 or 3 F atoms) and -O-(C<sub>1</sub>-C<sub>4</sub> alkyl) (optionally substituted with 1, 2 or 3 F atoms).

5

In a preferred embodiment of the present invention, when R<sub>1</sub> is a group of formula (i) and r is 0, Z is H.

A particular embodiment of the present invention is a compound of formula (I')

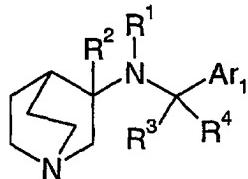


10

(I')

wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and Ar<sub>1</sub> have the values defined in formula (I) above.

Another particular embodiment of the present invention is a compound of formula (I'')



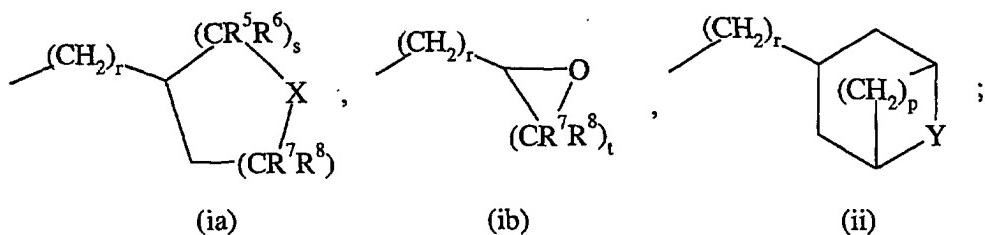
15

(I'')

wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and Ar<sub>1</sub> have the values defined in formula (I) above.

In a preferred embodiment of the present invention R<sup>1</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, -  
20 (CH<sub>2</sub>)<sub>m</sub>-CF<sub>3</sub>, -(CH<sub>2</sub>)<sub>n</sub>-S-(C<sub>1</sub>-C<sub>3</sub> alkyl), -CH<sub>2</sub>-COO-(C<sub>1</sub>-C<sub>2</sub> alkyl), -(C<sub>1</sub>-C<sub>5</sub> alkylene)-O-(C<sub>1</sub>-C<sub>3</sub> alkyl), -(C<sub>1</sub>-C<sub>5</sub> alkylene)-O-(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), -(C<sub>1</sub>-C<sub>5</sub> alkylene)-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>3</sub> alkyl), -(C<sub>1</sub>-C<sub>5</sub> alkylene)-OCF<sub>3</sub>, -(C<sub>1</sub>-C<sub>6</sub> alkylene)-OH, -(C<sub>1</sub>-C<sub>5</sub> alkylene)-CN, -(CH<sub>2</sub>)<sub>q</sub>-Ar<sub>2</sub> or a group of formula (ia), (ib) or (ii)

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$R^2, R^3, R^4, R^5, R^6, R^7, R^8, -X-, -Y-, p, q, r$  and  $s$  have the values defined above;

$m$  is 1, 2 or 3;

5     $n$  is 1, 2 or 3;

$t$  is 2, 3 or 4;

- $Ar_1$  is phenyl, pyridyl, thiazolyl or naphthyl; wherein said phenyl, pyridyl or thiazolyl group may be substituted with 1, 2 or 3 substituents each independently selected from halo, trifluoromethyl, cyano,  $C_1-C_4$  alkyl,  $-O-(C_1-C_4$  alkyl),  $-O-(C_1-C_4$  difluoroalkyl),  $-O-$

10    ( $C_1-C_4$  trifluoroalkyl),  $-S-(C_1-C_4$  alkyl),  $-S-(C_1-C_2$  trifluoroalkyl) and/or with 1 substituent selected from pyridyl, pyrazole, phenyl (optionally substituted with 1, 2 or 3 halo substituents) and phenoxy (optionally substituted with 1, 2 or 3 halo substituents); and wherein said naphthyl group may be optionally substituted with 1, 2 or 3 substituents each independently selected from halo, trifluoromethyl, cyano,  $C_1-C_4$  alkyl,  $-O-(C_1-C_4$

15    alkyl),  $-O-(C_1-C_4$  difluoroalkyl),  $-O-(C_1-C_4$  trifluoroalkyl),  $-S-(C_1-C_4$  alkyl),  $-S-(C_1-C_2$  trifluoroalkyl);

$Ar_2$  is naphthyl, pyridyl, thiazolyl, furyl, thiophenyl, benzothiophenyl, or phenyl, wherein said naphthyl, pyridyl, thiazolyl, furyl, thiophenyl, benzothiophenyl, or phenyl may be substituted with 1, 2 or 3 substituents each independently selected from halo,  $C_1-C_4$  alkyl,

20    trifluoromethyl and  $-O-(C_1-C_4$  alkyl).

In a preferred embodiment of the present invention  $R^2$  is hydrogen. In another preferred embodiment of the present invention  $R^3$  and  $R^4$  are hydrogen. More preferably  $R^2, R^3$  and  $R^4$  are hydrogen.

25

In a preferred embodiment of the present invention each  $R^5$  and  $R^6$  is hydrogen. In another preferred embodiment of the present invention each  $R^7$  and  $R^8$  is hydrogen. More

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preferably R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are hydrogen.

- In a preferred embodiment of the present invention R<sup>1</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl. More preferably R<sup>1</sup> is n-propyl, 1-methylethyl (i-propyl), 2-methylpropyl (i-butyl), 2-methylbutyl, 2,2-dimethylbutyl.
- 5

In another preferred embodiment of the present invention R<sup>1</sup> is -(C<sub>4</sub>-C<sub>5</sub> alkylene)-OH. More preferably R<sup>1</sup> is 2,2-dimethyl-2-hydroxyethyl or 3,3-dimethyl-3-hydroxypropyl.

- 10 In another preferred embodiment of the present invention R<sup>1</sup> is a group of formula (i) and each R<sup>5</sup> and R<sup>6</sup> is hydrogen. More preferably each R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> is hydrogen.

In another preferred embodiment of the present invention R<sup>1</sup> is a group of formula (ii) and each R<sup>5</sup> and R<sup>6</sup> is hydrogen. More preferably each R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> is hydrogen.

- 15
- In another preferred embodiment of the present invention R<sup>1</sup> is a group of formula (i), r is 0 or 1, s is 2, t is 1 or 2, -Z is hydrogen and -X- is -O-, -S- or -SO<sub>2</sub>- . More preferably R<sup>1</sup> is a group of formula (i), r is 0 or 1, s is 2, t is 1 or 2, -Z is hydrogen and -X- is -O-, for example tetrahydro-2H-pyran-4-yl, tetrahydrofuran-3-yl or (tetrahydrofuran-3-yl)methyl.
- 20 Most preferably R<sup>1</sup> is a group of formula (i), r is 0, s is 2, t is 1 or 2, -Z is hydrogen and -X- is -O-, for example tetrahydro-2H-pyran-4-yl or tetrahydrofuran-3-yl.

- In another preferred embodiment of the present invention R<sup>1</sup> is a group of formula (i), r is 0, s is 1, 2 or 3, t is 1, -Z is hydrogen and -X- is -CH<sub>2</sub>-, for example cyclobutyl, cyclopentyl or cyclohexyl.
- 25

In another preferred embodiment of the present invention R<sup>1</sup> is a group of formula (i), r is 1, s is 0, 1, 2 or 3, t is 1, -Z is hydrogen and -X- is -CH<sub>2</sub>-.

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In another preferred embodiment of the present invention R<sup>1</sup> is a group of the formula (ia). More preferably R<sup>1</sup> is a group of the formula (ia) and each R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> is hydrogen.

- 5 In another preferred embodiment of the present invention R<sup>1</sup> is a group of the formula (ib). More preferably R<sup>1</sup> is a group of the formula (ib), r is 1, t is 3, and each R<sup>7</sup> and R<sup>8</sup> is hydrogen.

- 10 In another preferred embodiment of the present invention R<sup>1</sup> is -(CH<sub>2</sub>)<sub>m</sub>-CF<sub>3</sub>. More preferably R<sup>1</sup> is -(CH<sub>2</sub>)<sub>m</sub>-CF<sub>3</sub> and m is 1, 2, or 3.

In another preferred embodiment of the present invention R<sup>1</sup> is -(CH<sub>2</sub>)<sub>n</sub>-S-(C<sub>1</sub>-C<sub>3</sub> alkyl). More preferably R<sup>1</sup> is -(CH<sub>2</sub>)<sub>3</sub>-S-CH<sub>3</sub>.

- 15 In another preferred embodiment of the present invention R<sup>1</sup> is -CH<sub>2</sub>-COO-(C<sub>1</sub>-C<sub>2</sub> alkyl). More preferably R<sup>1</sup> is -CH<sub>2</sub>-COOCH<sub>3</sub>.

In another preferred embodiment of the present invention R<sup>1</sup> is -(C<sub>1</sub>-C<sub>5</sub> alkylene)-O-(C<sub>1</sub>-C<sub>3</sub> alkyl). More preferably R<sup>1</sup> is -(C<sub>3</sub>-C<sub>4</sub> alkylene)-OCH<sub>3</sub>.

- 20 In another preferred embodiment of the present invention R<sup>1</sup> is -(C<sub>1</sub>-C<sub>5</sub> alkylene)-O-(C<sub>3</sub>-C<sub>6</sub> cycloalkyl). More preferably R<sup>1</sup> is -CH<sub>2</sub>-CH<sub>2</sub>-O-cyclobutyl.

- 25 In another preferred embodiment of the present invention R<sup>1</sup> is -(C<sub>1</sub>-C<sub>5</sub> alkylene)-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>3</sub> alkyl).

In another preferred embodiment of the present invention R<sup>1</sup> is -(C<sub>1</sub>-C<sub>5</sub> alkylene)-OCF<sub>3</sub>. More preferably R<sup>1</sup> is -CH<sub>2</sub>-CH<sub>2</sub>-OCF<sub>3</sub>.

- 30 In another preferred embodiment of the present invention R<sup>1</sup> is -(C<sub>1</sub>-C<sub>5</sub> alkylene)-CN. More preferably R<sup>1</sup> is -(C<sub>2</sub>-C<sub>4</sub> alkylene)-CN. Most preferably -CH<sub>2</sub>-CH<sub>2</sub>-CN or

-CH<sub>2</sub>-C(CH<sub>3</sub>)<sub>2</sub>-CN.

- In another preferred embodiment of the present invention R<sup>1</sup> is -(CH<sub>2</sub>)<sub>q</sub>-Ar<sub>2</sub>, and q is 1. More preferably R<sup>1</sup> is -(CH<sub>2</sub>)<sub>q</sub>-Ar<sub>2</sub>, q is 1 and -Ar<sub>2</sub> is pyridyl, phenyl or phenyl substituted  
5 with 1, 2 or 3 substituents each independently selected from halo, trifluoromethyl, C<sub>1</sub>-C<sub>4</sub> alkyl or O-(C<sub>1</sub>-C<sub>4</sub> alkyl).
- In another preferred embodiment of the present invention -Ar<sub>1</sub> is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo,  
10 trifluoromethyl and C<sub>1</sub>-C<sub>4</sub> alkyl and/or with 1 substituent selected from phenyl, phenyl substituted with 1, 2 or 3 halo substituents, pyridyl, pyrazole, phenoxy and phenoxy substituted with 1, 2 or 3 halo substituents; pyridyl; or pyridyl substituted with 1, 2 or 3 substituents each independently selected from halo, trifluoromethyl and C<sub>1</sub>-C<sub>4</sub> alkyl and/or with 1 substituent selected from phenyl and phenyl substituted with 1, 2 or 3 halo  
15 substituents. More preferably -Ar<sub>1</sub> is phenyl or phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, trifluoromethyl and C<sub>1</sub>-C<sub>4</sub> alkyl and/or with 1 substituent selected from phenyl, phenyl substituted with 1, 2 or 3 halo substituents, pyridyl, pyrazole, phenoxy and phenoxy substituted with 1, 2 or 3 halo substituents. Most preferably -Ar<sub>1</sub> is phenyl substituted with 1 or 2 substituents each  
20 independently selected from halo, trifluoromethyl and C<sub>1</sub>-C<sub>4</sub> alkyl and/or with 1 substituent selected from phenyl, phenyl substituted with 1, 2 or 3 halo substituents, pyridyl, pyrazole, phenoxy and phenoxy substituted with 1, 2 or 3 halo substituents. Suitable -Ar<sub>1</sub> groups include, for example, 2-methylthiophenyl, 2-methylphenyl, 2-fluorophenyl, 2-chlorophenyl, 2-isopropoxyphenyl, 2-trifluoromethylphenyl, 2-difluoromethoxyphenyl, 2-methoxyphenyl, 2-ethoxyphenyl, 2-(1,1'-biphenyl), 2-phenoxyphenyl, 2-benzylphenyl, 3-trifluoromethoxyphenyl, 3-chlorophenyl, 3-trifluoromethylphenyl, 3-methylphenyl, 3-trifluorothiomethoxyphenyl, 3-methoxyphenyl, 4-trifluoromethylphenyl, 4-chlorophenyl, 4-fluorophenyl, 3,5-dichlorophenyl, 3,5-dimethylphenyl, 3-trifluoromethyl-5-fluorophenyl, 3,5-difluorophenyl, 2,3-dichlorophenyl, 2,3-dimethylphenyl, 2-chloro-3-trifluoromethylphenyl, 2-chloro-3-methylphenyl, 2-methyl-3-chlorophenyl, 2,4-dichlorophenyl, 2,4-dimethyl, 2,4-

difluorophenyl, 2-chloro-4-fluorophenyl, 2-trifluoromethyl-4-fluorophenyl, 2-fluoro-4-trifluoromethylphenyl, 2-methyl-4-chlorophenyl, 2-methoxy-4-fluorophenyl, 2-trifluoromethyl-5-fluorophenyl, 2,5-dimethylphenyl, 4-fluoro-[1,1'-biphenyl]-2-yl, 2-chloro-5-fluorophenyl, 2-(trifluoromethyl)-6-fluorophenyl, 2-chloro-6-fluorophenyl, 3,4-dichlorophenyl, and 3-chloro-4-fluorophenyl. In general when  $-Ar_1$  is phenyl substituted with pyridyl, 3-pyridyl is preferred.

In another preferred embodiment of the present invention  $-Ar_1$  is pyridyl or pyridyl substituted with 1, 2 or 3 substituents each independently selected from halo, trifluoromethyl and C<sub>1</sub>-C<sub>4</sub> alkyl and/or with 1 substituent selected from phenyl and phenyl substituted with 1, 2 or 3 halo substituents. More preferably  $-Ar_1$  is pyridyl substituted with 1 or 2 substituents each independently selected from halo, trifluoromethyl and C<sub>1</sub>-C<sub>4</sub> alkyl and/or with 1 substituent selected from phenyl and phenyl substituted with 1, 2 or 3 halo substituents. Suitable  $-Ar_1$  groups include, for example, 3-phenyl-2-pyridyl. In general when  $-Ar_1$  is a substituted pyridyl, substituted 2-pyridyl is preferred.

Illustrative of the present invention are the compounds identified below or their pharmaceutically acceptable salts:

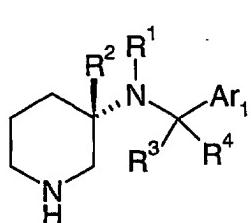
- (3*S*)-*N*-(2-Methylpropyl)-*N*-{[2-(trifluoromethyl)-phenyl]methyl}piperidin-3-amine,
- (3*S*)-*N*-(3,3-Dimethylbutyl)-*N*-{[2-(trifluoromethyl)-phenyl]methyl}piperidin-3-amine,
- (3*S*)-*N*-Cyclohexyl-*N*-{[2-(trifluoromethyl)phenyl]-methyl}piperidin-3-amine,
- (3*S*)-*N*-{[5-Fluoro-2-(trifluoromethyl)phenyl]methyl}-*N*-tetrahydro-2*H*-pyran-4-ylpiperidin-3-amine,
- (3*S*)-*N*-[(2-Chloro-5-fluorophenyl)methyl]-*N*-tetrahydro-2*H*-pyran-4-ylpiperidin-3-amine,
- (3*S*)-*N*-{[1,1'-Biphenyl]-2-ylmethyl}-*N*-tetrahydro-2*H*-pyran-4-ylpiperidin-3-amine,
- (3*S*)-*N*-[(2-Chlorophenyl)methyl]-*N*-tetrahydro-2*H*-pyran-4-ylpiperidin-3-amine,
- (3*S*)-*N*-Tetrahydro-2*H*-pyran-4-yl-*N*-{[2-(trifluoromethyl)phenyl]methyl}piperidin-3-amine,
- (3*S*)-*N*-Cyclopentyl-*N*-{[2-(trifluoromethyl)phenyl]-methyl}piperidin-3-amine,
- (3*S*)-*N*-{[1,1'-Biphenyl]-2-ylmethyl}-*N*-cyclopentyl-piperidin-3-amine,
- (3*S*)-*N*-Cyclopentyl-*N*-{[5-fluoro-1,1'-biphenyl]-2-ylmethyl}-piperidin-3-amine,

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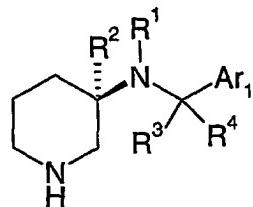
- (3*S*)-*N*-(Tetrahydrofuran-3-ylmethyl)-*N*-{[2-(trifluoromethyl)phenyl]methyl}piperidin-3-amine,
- N*-{[2-(Methyloxy)phenyl]methyl}-*N*-{[2-(trifluoromethyl)phenyl]methyl}piperidin-3-amine,
- 5   *N*-Cyclohexyl-*N*-{[2-(trifluoromethyl)phenyl]methyl}-piperidin-3-amine,  
*N*-(Phenylmethyl)-*N*-{[2-(trifluoromethyl)phenyl]-methyl}piperidin-3-amine,  
(3*S*)-*N*-(2-Methylpropyl)-*N*-{[2-(trifluoromethyl)phenyl]-methyl}-1-azabicyclo[2.2.2]octan-3-amine,
- 10   (3*S*)-*N*-{[1,1'-Biphenyl]-2-ylmethyl}-*N*-(2-methylpropyl)-1-azabicyclo[2.2.2]octan-3-amine,
- (3*S*)-*N*-{[(3,5-Dichlorophenyl)methyl]-*N*-(2-methylpropyl)-1-azabicyclo[2.2.2]octan-3-amine,
- (3*S*)-*N*-{[(2,4-Dichlorophenyl)methyl]-*N*-(2-methylpropyl)-1-azabicyclo[2.2.2]octan-3-amine,
- 15   (3*S*)-*N*-{[4-Fluoro-2-(trifluoromethyl)phenyl]methyl}-*N*-(2-methylpropyl)-1-azabicyclo[2.2.2]octan-3-amine, and  
(3*S*)-*N*-{[(4-Fluoro[1,1'-biphenyl]-2-yl)methyl]-*N*-(2-methylpropyl)-1-azabicyclo[2.2.2]octan-3-amine.
- 20   The present invention includes pharmaceutically acceptable salts of the compounds of formula (I). Suitable salts include acid addition salts, including salts formed with inorganic acids (for example hydrochloric, hydrobromic, nitric, sulphuric or phosphoric acid) or with organic acids, such as organic carboxylic acids (for example acetic, fumaric, pyruvic, lactobionic, glycolic, oxalic, maleic, hydroxymaleic, malic, citric, salicylic, o-acetoxybenzoic or tartaric acid), or organic sulphonic acids (for example toluene-p-sulphonic, naphthalenesulfonic, bisethanesulphonic or methanesulphonic acid). Particularly preferred are salts formed with phosphoric, fumaric, L-tartaric, D-tartaric or naphthalenesulfonic acid. Most preferred are salts formed with L-tartaric or D-tartaric acid.
- 25

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- It will be appreciated that certain compounds of formula (I) may possess one or more chiral centres. Where a structural formula does not specify the stereochemistry at one or more chiral centres, it encompasses all possible stereoisomers and all possible mixtures of stereoisomers (including, but not limited to, racemic mixtures), which may result from 5 stereoisomerism at each of the one or more chiral centers. For example, the carbon atom at the three position of the piperidine ring of compounds of formula (I') can give rise to two enantiomers of formulae (Ia) and (Ib):

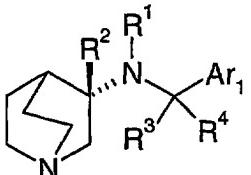


(Ia)

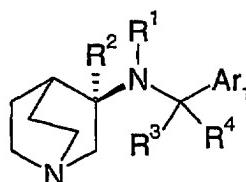


(Ib)

- 10 wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and Ar<sub>1</sub> have the values defined in formula (I) above. Said isomers are also an aspect of the present invention. Preferred compounds of the invention are those of formula (Ia). In the same way, the carbon atom at the three position of the quinuclidine ring of compounds of formula (I'') can give rise to two enantiomers of formulae (Ic) and (Id):



(Ic)



(Id)

15

wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and Ar<sub>1</sub> have the values defined in formula (I) above. Said isomers are also an aspect of the present invention. Preferred compounds of the invention are those of formula (Ic).

20

The preferred stereochemistry detailed above also applies to the compounds used as intermediates for the preparation of the compounds of the present invention.

As mentioned above, the compounds of the present invention and their pharmaceutically acceptable salts inhibit the uptake of one or more of the monoamine neurotransmitters serotonin, dopamine and norepinephrine. In view of these properties, the compounds of the present invention and their pharmaceutically acceptable salts are indicated for use in

5 treating disorders which are caused by or linked to decreased neurotransmission of one or more of these monoamines. Such disorders include disorders of the central and/or peripheral nervous system.

One preferred group of compounds of the present invention selectively inhibit the  
10 reuptake of serotonin and norepinephrine over dopamine. Preferably said group of compounds of the present invention selectively inhibit the serotonin and norepinephrine transporters relative to the dopamine transporter by a factor of at least five, and even more preferably by a factor of at least ten. Compounds of the present invention with this pharmacological profile are particularly useful for the treatment of depression, eating  
15 disorders (including bulimia and anorexia nervosa), inflammatory bowel disorders, functional bowel disorders, dyspepsia, Crohn's disease, ileitis, ischemic bowel disease, ulcerative colitis, gastroesophageal reflux for functional bowel disorders, irritable bowel syndrome, obesity, interstitial cystitis, urethral syndrome, gastric motility disorders, substance abuse (including alcoholism, tobacco abuse, symptoms caused by withdrawal  
20 or partial withdrawal from the use of tobacco or nicotine and drug addiction including cocaine abuse), pain (including inflammatory pain, neuropathic pain, non-neuropathic non-inflammatory pain, persistent pain, persistent pain of inflammatory and/or neuropathic origin, headache and migraine), incontinence (including stress urinary incontinence and urge incontinence), dementia of ageing, senile dementia, Alzheimer's,  
25 memory loss, Parkinsonism, attention-deficit disorder (including attention-deficit hyperactivity disorder), anxiety, social phobia, disruptive behavior disorders, impulsive control disorders, borderline personality disorder, chronic fatigue syndrome, panic disorders, obsessive compulsive disorder, post-traumatic stress disorder, schizophrenia, gastrointestinal disorders, cardiovascular disorders, hot flushes/flashes, emesis, sleep  
30 disorders, cognitive disorders, psychotic disorders, brain trauma, premenstrual syndrome or late luteal syndrome, sexual dysfunction (including premature ejaculation and erectile

difficulty), autism, mutism and trichotillomania. They are more particularly useful for the treatment of depression, incontinence (particularly stress urinary incontinence) and pain (particularly persistent pain). They are most particularly useful for the treatment of persistent pain.

5

For clinical purposes, pain may be divided into two categories: acute pain and persistent pain. Acute pain is provoked by noxious stimulation produced by injury and/or disease of skin, deep somatic structures or viscera, or abnormal function of muscle or viscera that does not produce actual tissue damage. On the other hand, persistent pain can be defined

- 10 as pain that persists beyond the usual course of an acute disease or a reasonable time for an injury to heal or that is associated with a chronic pathologic process that causes continuous pain or the pain recurs at intervals for months or years. If pain is still present after a cure should have been achieved, it is considered persistent pain. For the purpose of the present invention, persistent pain can be chronic non-remitting or recurrent. The  
15 difference in definition between acute and persistent pain is not merely semantic but has an important clinical relevance. For example, a simple fracture of the wrist usually remains painful for a week to 10 days. If the pain is still present beyond the typical course of treatment, it is likely that the patient is developing reflex sympathetic dystrophy, a persistent pain syndrome that requires immediate effective therapy. Early  
20 and effective intervention potentially prevents the undue disability and suffering, and avoids the potential development of a condition that becomes refractory to therapy.

- Acute and persistent pain differ in etiology, mechanisms, pathophysiology, symptomatology, diagnosis, therapy, and physiological responses. In contrast to the  
25 transitory nature of acute pain, persistent pain is caused by chronic pathologic processes in somatic structures or viscera, by prolonged and sometimes permanent dysfunction of the peripheral or central nervous system, or both. Also, persistent pain can sometimes be attributed to psychologic mechanisms and/or environmental factors.  
30 More specifically, persistent pain can be segmented into neuropathic pain (e.g. diabetic neuropathy, infectious neuropathic pain associated with AIDS, non-surgical carpal tunnel

- syndromes, post-herpetic neuralgia, cervical, thoracic and lumbosacral radiculopathies, stroke-related central pains, trigeminal neuralgia and complex regional pain syndromes I and II), inflammatory pain (e.g. polymyalgia, rheumatoid arthritis and osteoarthritis), and non-neuropathic non-inflammatory pain, non-neuropathic non-inflammatory chronic pain
- 5 (NNNCP) (e.g. chronic fatigue syndrome, chronic back pain without radiculopathy, fibromyalgia, chronic tension type headaches, inflammatory bowel disorders, irritable bowel syndrome, whiplash injuries, chronic pelvic pain, temporomandibular joint disorder (TMJD) and failed back).
- 10 Current therapies for persistent pain include opiates, barbiturate-like drugs such as thiopental sodium and surgical procedures such as neurectomy, rhizotomy, cordotomy, and corpectomy.
- 15 Another preferred group of compounds of the present invention selectively inhibit the reuptake of norepinephrine over serotonin and dopamine. Preferably said group of compounds of the present invention selectively inhibit the norepinephrine transporter relative to the serotonin and dopamine transporters by a factor of at least five, and even more preferably by a factor of at least ten. Compounds of the present invention with this pharmacological profile are particularly useful for the treatment of addictive disorder and
- 20 withdrawal syndrome, an adjustment disorder (including depressed mood, anxiety, mixed anxiety and depressed mood, disturbance of conduct, and mixed disturbance of conduct and mood), an age-associated learning and mental disorder (including Alzheimer's disease), alcohol addiction, anorexia nervosa, apathy, an attention-deficit disorder (ADD) due to general medical conditions, attention-deficit hyperactivity disorder (ADHD)
- 25 including the predominantly inattentive type of ADHD and the predominantly hyperactive-impulsive type of ADHD, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, chronic or acute stress, cognitive disorders (discussed in more detail below but including mild cognitive impairment (MCI) and cognitive impairment associated with schizophrenia (CIAS)), communication disorders (including stuttering, expressive
- 30 language disorder, mixed receptive-expressive language disorder, phonological disorder and communication disorder not otherwise specified), conduct disorder, cyclothymic

disorder, dementia of the Alzheimers type (DAT), depression (including adolescent depression and minor depression), dysthymic disorder, emotional dysregulation (including emotional dysregulation associated with ADHD, borderline personality disorder, bipolar disorder, schizophrenia, schizoaffective disorder and intermittent explosive disorder), fibromyalgia and other somatoform disorders (including somatization disorder, conversion disorder, pain disorder, hypochondriasis, body dysmorphic disorder, undifferentiated somatoform disorder, and somatoform NOS), generalized anxiety disorder (GAD), hot flashes or vasomotor symptoms, hypotensive states including orthostatic hypotension, impulse control disorders (including intermittent explosive disorder, kleptomania, pyromania, pathological gambling, trichotillomania and impulse-control disorder not otherwise specified), incontinence (i.e., stress incontinence, genuine stress incontinence, and mixed incontinence), an inhalation disorder, an intoxication disorder, learning disabilities (including developmental speech and language disorders (such as developmental articulation disorder, developmental expressive language disorder and developmental receptive language disorder), learning disorders (such as reading disorder, mathematics disorder, disorder of written expression and learning disorder not otherwise specified) and motor skills disorders (such as developmental coordination disorder)), mania, migraine headaches, nicotine addiction, obesity (i.e., reducing the weight of obese or overweight patients), obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorder, pain including chronic pain, neuropathic pain and antinociceptive pain, panic disorder, peripheral neuropathy, post-traumatic stress disorder, personality change due to a general medical condition (including labile type, disinhibited type, aggressive type, apathetic type, paranoid type, combined type and unspecified type), pervasive developmental disorders (including autistic disorder, Asperger's disorder, Rett's disorder, childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified), premenstrual dysphoric disorder (i.e., premenstrual syndrome and late luteal phase dysphoric disorder), psoriasis, a psychoactive substance use disorder, a psychotic disorder (including schizophrenia, schizoaffective and schizophreniform disorders), seasonal affective disorder, selective serotonin reuptake inhibition (SSRI) "poop out" syndrome (i.e., wherein a patient who fails to maintain a satisfactory response to SSRI therapy after an initial period of

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satisfactory response), a sleep disorder (such as narcolepsy and enuresis), social phobia (including social anxiety disorder), a specific developmental disorder, TIC disorders (e.g., Tourette's Disease), tobacco addiction and vascular dementia. They are most particularly useful for the treatment of ADHD and schizophrenia.

5

The term "cognitive disorders" (also variously referred to as "cognitive failure," "cognitive insufficiency," "cognitive deficit," "cognitive impairment," "cognitive dysfunction," and the like) refers to the dysfunction, diminution, or loss of one or more cognitive functions, the processes by which knowledge is acquired, retained, and used.

- 10 Cognitive dysfunction includes cognitive changes associated with ageing ("age-associated memory impairment"), as well as changes due to other causes. Cognitive impairment is most commonly due to a delirium or dementia, but can also occur in association with a number of other medical or neuropsychiatric disorders. More focal cognitive deficits are diagnosed using the criteria disclosed in the *Diagnostic and Statistical Manual of Mental*  
15 *Disorders*, Fourth Edition, Text Revision (DSM-IV-TR™, 2000), American Psychiatric Association, Washington, D.C., as either amnestic disorders (affecting memory) or cognitive disorder not otherwise specified (NOS), which includes executive dysfunction, visuospatial/visuoconstructional impairment, attentional deficits, disorientation, etc. These more focal cognitive disorders also have a wide variety of causes, some of which are of  
20 unknown etiology.

- A delirium is characterized by a disturbance of consciousness with a reduced ability to focus, sustain, or shift attention and a change in cognition that develops over a short period of time. Delirium is very common, and occurs on average in about a fifth of  
25 general hospital inpatients, and is even more common in nursing home patients and those with terminal illnesses. The disorders included in the "Delirium" section of the DSM-IV-TR™ are listed according to presumed etiology: Delirium Due to a General Medical Condition, Substance-Induced Delirium (i.e., due to a drug of abuse, a medication, or toxin exposure), Delirium Due to Multiple Etiologies, or Delirium Not Otherwise  
30 Specified (if the etiology is indeterminate). As disclosed by Wise et al. ((2002) *Delirium (Confusional States)*, In Wise and Rundell, Eds., *The American Psychiatric Publishing*

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*Textbook of Consultation-Liaison Psychiatry, Psychiatry in the Medically Ill*, Second Edition, American Psychiatric Publishing, Inc., Washington, D.C., Chapter 15, pp. 257-272, Table 15-4), exemplary etiological bases of delirium include, but are not limited to, infection, withdrawal from alcohol and drugs, acute metabolic conditions, trauma of 5 various types, CNS pathologies, hypoxia, vitamin deficiencies, endocrinopathies, acute vascular conditions, toxins or drugs, and heavy metals.

A dementia is a chronic condition, usually with a more gradual deterioration of memory and other intellectual functioning and other cognitive skills severe enough to interfere 10 with the ability to perform activities of daily living. Although dementia may occur at any age, it primarily affects the elderly, presenting in more than 15% of persons over 65 years of age and in as many as 40% of persons over 80 years old. Dementia due to Alzheimer's disease is particularly common. Non-Alzheimer's cognitive impairments and/or dementias include, for example, those caused by or associated with: vascular diseases; 15 Parkinson's disease; Lewy body disease (diffuse Lewy body disease); HIV/AIDS; mild cognitive impairments; mild nuerocognitive disorders; age-associated memory impairments; neurologic and/or psychiatric conditions including epilepsy and epilepsy treatments; brain tumors, cysts, lesions, or other inflammatory brain diseases; multiple sclerosis; Down's syndrome; Rett's syndrome; progressive supranuclear palsy; frontal 20 lobe dementia syndromes; schizophrenia and related psychiatric disorders; antipsychotic medications; traumatic brain injury (closed head injury), dementia pugilistica, and other head traumas; normal-pressure hydrocephalus; surgery (including coronary artery by-pass graft surgery) and anaesthesia, electroconvulsive shock therapy, and cancer and cancer therapies.

25 The dementias are also listed in the "Dementia" section of the DSM-IV-TR™ according to presumed etiology: Dementia of the Alzheimer's Type, Vascular Dementia, Dementia Due to Other General Medical Conditions (e.g., human immunodeficiency virus [HIV] disease, head trauma, Parkinson's disease, Huntington's disease), Substance-Induced 30 Persisting Dementia (i.e., due to a drug of abuse, a medication, or toxin exposure), Dementia Due to Multiple Etiologies, or Dementia Not Otherwise Specified (if the

etiology is indeterminate). As disclosed by Gray and Cummings ((2002) *Dementia*, In Wise and Rundell, Eds., *The American Psychiatric Publishing Textbook of Consultation-Liaison Psychiatry, Psychiatry in the Medically Ill*, Second Edition, American Psychiatric Publishing, Inc., Washington, D.C., Chapter 16, pp. 273-306, Table 16-1), exemplary

- 5 etiological bases of principal dementia syndromes include, but are not limited to, degenerative disorders (cortical and subcortical), vascular disorders, myelinoclastic disorders, traumatic conditions, neoplastic disorders, hydrocephalic disorders, inflammatory conditions, infections, toxic conditions, metabolic disorders, and psychiatric disorders.

10

An amnestic disorder is characterized by memory impairment in the absence of other significant accompanying cognitive impairments. The disorders in the "Amnestic Disorders" section of the DSM-IV-TR™ are also listed according to presumed etiology: Amnestic Disorder Due to a General Medical Condition, Substance-Induced Persisting

- 15 Amnestic Disorder, or Amnestic Disorder Not Otherwise Specified.

Cognitive Disorder Not Otherwise Specified in the DSM-IV-TR™ covers presentations that are characterized by cognitive dysfunction presumed to be due to either a general medical condition or substance use that do not meet criteria for any of the disorders listed  
20 elsewhere in the section of the DSM-IV-TR™ entitled "Delirium, Dementia, and Amnestic and Other Cognitive Disorders."

- Dementia, amnestic disorders, and cognitive disorders NOS occur in patients with a wide variety of other disorders including, but not limited to, Huntington's disease (chorea);  
25 Pick's disease; spinocerebellar ataxias (types 1-11); corticobasalganglionic degeneration; neuroacanthocytosis; dentatorubropallidolysian atrophy (DRPLA); systemic lupus erythematosus; heavy metal intoxication; alcoholic dementia (Wernicke's encephalopathy); fetal alcohol syndrome; single or multiples strokes, including small vessels (Binswanger's dementia: subcortical arteriosclerotic encephalopathy) and large vessels (multi-infarct dementia); anoxic encephalopathy; tumors; birth anoxia; premature birth; inborn errors of metabolism; neurofibromatosis (Type I); tuberous sclerosis;

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Hallervorden Spatz disease; Wilson's disease; post-infectious sequelae (e.g., tuberculosis, viral encephalitis, bacterial meningitis); subdural hematoma; subcortical dementia; Creutzfeldt-Jakob disease; Gerstmann-Sträussler-Scheinker disease; general paresis; and syphilis.

5

As discussed in detail above, cognitive failure may present in patients suffering from a number of disorders, including dementia or delirium, or due to a wide variety of other causes. The compounds of the present invention are useful for the treatment or prevention of cognitive failure associated with, or due to, the disorders or etiologies

10 discussed above, including disorders formally classified in the DSM-IV-TR™. For the convenience of the reader, the DSM-IV-TR™ code numbers or descriptions are supplied below. "ICD-9-CM codes" refers to codes for, e.g., selected general medical conditions and medication-induced disorders contained in the *International Classification of Diseases, 9<sup>th</sup> Revision, Clinical Modification*.

15

Delirium Due to a General Medical Condition 293.0

Substance-Induced Delirium, including:

20 Substance Intoxication Delirium:

*Code [Specific Substance] Intoxication Delirium:*

(291.0 Alcohol; 292.81 Amphetamine [or Amphetamine-Like Substance]; 292.81 Cannabis; 292.81 Cocaine; 292.81 Hallucinogen; 292.81 Inhalant; 292.81 Opioid; 292.81 Phencyclidine [or Phencyclidine-Like Substance]; 292.81 Sedative,

25 Hypnotic, or Anxiolytic; 292.81 Other [or Unknown] Substance [e.g., cimetidine, digitalis, benztropine])

Substance Withdrawal Delirium:

*Code [Specific Substance] Withdrawal Delirium:*

30 (291.0 Alcohol; 292.81 Sedative, Hypnotic, or Anxiolytic; 292.81 Other [or Unknown] Substance)

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**Delirium Due to Multiple Etiologies:**

Multiple codes are used, reflecting the specific delirium and specific etiologies,  
e.g., 293.0 Delirium Due to Viral Encephalitis; 291.0 Alcohol Withdrawal Delirium

5

Delirium Not Otherwise Specified	780.09
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Dementia of the Alzheimer's Type	294.1x* (*ICD-9-CM code)
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Subtypes:

10	With Early Onset (onset of the dementia is age 65 years or under)	
	With Late Onset (onset of the dementia is after age 65 years)	
	Without Behavioral Disturbance	294.10
	With Behavioral Disturbance	294.11

15	Vascular Dementia	290.4x
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Subtypes:

20	With Delirium	290.41
	With Delusions	290.42
	With Depressed Mood	290.43
	With Behavioral Disturbance	Uncoded
	Uncomplicated	290.40

Dementia Due to HIV Disease	294.1x* (*ICD-9-CM code)
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25	Dementia Due to Head Trauma	294.1x* (*ICD-9-CM code)
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Dementia Due to Parkinson's Disease	294.1x* (*ICD-9-CM code)
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Dementia Due to Huntington's Disease	294.1x* (*ICD-9-CM code)
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30

Dementia Due to Pick's Disease	290.1x* (*ICD-9-CM code)
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Dementia Due to Creutzfeldt-Jakob Disease      290.1x\* (\*ICD-9-CM code)

Dementia Due to Other General Medical Conditions 294.1x\* (\*ICD-9-CM code)

5      Code based on presence or absence of a clinically significant behavioral disturbance:

Without Behavioral Disturbance      294.10

With Behavioral Disturbance      294.11

10     Substance-Induced Persisting Dementia

*Code [Specific Substance]-Induced Persisting Dementia:*

(291.2 Alcohol; 292.82 Inhalant; 292.82 Sedative, Hypnotic, or Anxiolytic;  
292.82 Other [or Unknown] Substance)

15     Dementia Due to Multiple Etiologies

Coding note: Use multiple codes based on specific dementias and specific etiologies, e.g., 294.10 Dementia of the Alzheimer's Type, With Late Onset, Without Behavioral Disturbance; 290.40 Vascular Dementia, Uncomplicated.

20     Dementia Not Otherwise Specified      294.8

Amnestic Disorder Due to a General Medical Condition      294.0

Transient or Chronic

25     Substance-Induced Persisting Amnestic Disorder

*Code [Specific Substance]-Induced Persisting Amnestic Disorder:*

291.1 Alcohol; 292.83 Sedative, Hypnotic, or Anxiolytic; 292.83 Other [or Unknown] Substance

30     Amnestic Disorder Not Otherwise Specified      294.8

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Cognitive Disorder Not Otherwise Specified 294.9

Age-Related Cognitive Decline 780.9

- 5 Examples of cognitive disorders due to various etiologies, or associated with various disorders, of particular interest that can be prevented or treated using the compounds of the present invention include: enhancing cognitive functions and executive functioning (ability to plan, initiate, organize, carry out, monitor, and correct one's own behavior) in normal subjects or in subjects exhibiting cognitive dysfunction; treatment of cognitive  
10 and attentional deficits associated with prenatal exposure to substances of abuse including, but not limited to, nicotine, alcohol, methamphetamine, cocaine, and heroin; treatment of cognitive impairment caused by chronic alcohol and drug abuse (substance-induced persisting dementia), medicament side effects, and treatment of drug craving and withdrawal; treatment of cognitive deficits in Down's Syndrome patients; treatment of  
15 deficits in normal memory functioning comorbid with major depressive and bipolar disorders; treatment of cognitive impairment associated with depression, mental retardation, bipolar disorder, or schizophrenia; treatment of dementia syndromes associated with mania, conversion disorder, and malingering; treatment of problems of attention, prefrontal executive function, or memory due to head trauma or stroke;  
20 treatment of cognitive dysfunction in menopausal and post-menopausal women and in women undergoing hormone replacement therapy; treatment of cognitive deficits and fatigue due to, or associated with, cancer and cancer therapies (cognitive deficits are associated with a variety of cancer treatments, including cranial radiation, conventional (standard-dose) chemotherapy, high-dose chemotherapy and hematopoietic (bone-marrow) transplantation, and biologic agents).  
25

Compounds which selectively inhibit the reuptake of norepinephrine over serotonin and dopamine are also useful in a method for treating a patient suffering from or susceptible to psychosis, comprising administering to said patient an effective amount of a first  
30 component which is an antipsychotic, in combination with an effective amount of a second component which is a compound of formula (I) that selectively inhibits the

reuptake of norepinephrine over serotonin and dopamine. The invention also provides a pharmaceutical composition which comprises a first component that is an antipsychotic, and a second component that is a compound of formula (I) that selectively inhibits the reuptake of norepinephrine over serotonin and dopamine. In the general expressions of  
5 this aspect of the present invention, the first component is a compound that acts as an antipsychotic. The antipsychotic may be either a typical antipsychotic or an atypical antipsychotic. Although both typical and atypical antipsychotics are useful for these methods and formulations of the present invention, it is preferred that the first component compound is an atypical antipsychotic.

10

Typical antipsychotics include, but are not limited to: Chlorpromazine, 2-chloro-10-(3-dimethylaminoprop-yl)phenothiazine, is described in U.S. Patent 2,645,640. Its pharmacology has been reviewed (Crismon, Psychopharma-col. Bul., **4**, 151 (October 1967); Droperidol, 1-(1-[3-(p-fluorobenzoyl)propyl]-1,2,3,6-tetrahydro-4-pyridyl)-2-  
15 benzimidazolinone, is described in U.S. Patent 3,141,823; Haloperidol, 4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl]-1-(4-fluorophenyl)-1-butanone, is described in U.S. Patent 3,438,991. Its therapeutic efficacy in psychosis has been reported (Beresford and Ward, Drugs, **33**, 31-49 (1987); Thioridazine, 1-hydroxy-10-[2-(1-methyl-2-pyridinyl)ethyl]-2-(methylthio)phenothiazine hydrochloride, was described by Bourquin,  
20 et al. (Helv. Chim. Acta, **41**, 1072 (1958)). Its use as an antipsychotic has been reported (Axelsson, et al., Curr. Ther. Res., **21**, 587 (1977)); and Trifluoperazine, 10-[3-(4-methyl-1-piperazinyl)-propyl]-2-trifluoromethylphenthiazine hydrochloride, is described in U.S. Patent 2,921,069.

25 Atypical antipsychotics include, but are not limited to: Olanzapine, 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine, is a known compound and is described in U.S. Patent No. 5,229,382 as being useful for the treatment of schizophrenia, schizophreniform disorder, acute mania, mild anxiety states, and psychosis; Clozapine, 8-chloro-11-(4-methyl-1-piperazinyl)-5H-  
30 dibenzo[b,e][1,4]diazepine, is described in U.S. Patent No. 3,539,573. Clinical efficacy in the treatment of schizophrenia is described (Hanes, et al., Psychopharmacol. Bull., **24**,

62 (1988)); Risperidone, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one, and its use in the treatment of psychotic diseases are described in U.S. Patent No. 4,804,663; Sertindole, 1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]-1-piperidinyl]ethyl]imidazolidin-2-one, is 5 described in U.S. Patent No. 4,710,500. Its use in the treatment of schizophrenia is described in U.S. Patent Nos. 5,112,838 and 5,238,945; Quetiapine, 5-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]ethanol, and its activity in assays which demonstrate utility in the treatment of schizophrenia are described in U.S. Patent 10 No. 4,879,288. Quetiapine is typically administered as its (E)-2-butenedioate (2:1) salt; Ziprasidone, 5-[2-[4-(1,2-benzoisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one, is typically administered as the hydrochloride monohydrate. The compound is described in U.S. Patent Nos. 4,831,031 and 5,312,925. Its activity in assays which demonstrate utility in the treatment of schizophrenia are described in U.S. Patent No. 4,831,031; and Aripiprazole (Abilify<sup>TM</sup>), 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyryl (U.S. Patents 4,734,416 and 5,006,528) is a 15 new antipsychotic indicated for the treatment of schizophrenia.

It will be understood that while the use of a single antipsychotic as a first component compound is preferred, combinations of two or more antipsychotics may be used as a first 20 component if necessary or desired. Similarly, while the use of a single compound of formula (I) as a second component compound is preferred, combinations of two or more compounds of formula (I) may be used as a second component if necessary or desired.

While all combinations of first and second component compounds are useful and 25 valuable, certain combinations are particularly valued and are preferred, as follows:

- olanzapine/compound of formula (I)
- clozapine/compound of formula (I)
- risperidone/compound of formula (I)
- sertindole/compound of formula (I)
- 30 quetiapine/compound of formula (I)
- ziprasidone/compound of formula (I)

## aripiprazole/compound of formula (I)

In general, combinations and methods of treatment using olanzapine as the first component are preferred. It is especially preferred that when the first component is 5 olanzapine, it will be the Form II olanzapine as described in U.S. Patent 5,736,541. It is further preferred that the Form II olanzapine polymorph will be administered as the substantially pure Form II olanzapine polymorph. As used herein "substantially pure" refers to Form II associated with less than about 5% Form I, preferably less than about 2% Form I, and more preferably less than about 1% Form I. Further, "substantially pure" 10 Form II will contain less than about 0.5% related substances, wherein "related substances" refers to undesired chemical impurities or residual solvent or water. In particular, "substantially pure" Form II should contain less than about 0.05% content of acetonitrile, more preferably, less than about 0.005% content of acetonitrile. Additionally, the polymorph of the invention should contain less than 0.5% of associated 15 water. Although Form II olanzapine is preferred it will be understood that as used herein, the term "olanzapine" embraces all solvate and polymorphic forms unless specifically indicated.

Conditions that can be treated by the adjunctive therapy aspect of the present invention 20 include schizophrenia, schizophreniform diseases, bipolar disorder, acute mania, and schizoaffective disorders. The titles given these conditions represent multiple disease states. The following list illustrates a number of these disease states, many of which are classified in the DSM-IV-TR™. The DSM-IV-TR™ code numbers for these disease states 25 are supplied below, when available, for the convenience of the reader.

25

Paranoid Type Schizophrenia	295.30
Disorganized Type Schizophrenia	295.10
Catatonic Type Schizophrenia	295.20
Undifferentiated Type Schizophrenia	295.90
Residual Type Schizophrenia	295.60
Schizophreniform Disorder	295.40

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Schizoaffective Disorder	295.70
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The present invention also encompasses the use of one or more compounds of formula (I) that selectively inhibit the reuptake of norepinephrine over serotonin and dopamine in combination with one or more conventional Alzheimer's agents for the prevention or treatment of cognitive dysfunction in patients suffering from Alzheimer's disease. The invention also provides a pharmaceutical composition which comprises a first component that is a conventional Alzheimer's agent and a second component that is a compound of formula (I) that selectively inhibits the reuptake of norepinephrine over serotonin and dopamine. Conventional Alzheimer's agents include inhibitors of acetylcholine degradation (i.e., cholinesterase or acetylcholinesterase inhibitors) within synapses, e.g., donepezil (Aricept®), rivastigmine (Exelon®), galantamine (Reminyl®), and tacrine (Cognex®); the selective monoamine oxidase inhibitor selegiline (Eldepryl®); and memantine (Namenda™), a newly FDA-approved NMDA receptor antagonist for the treatment of moderate to severe Alzheimer's disease. Modafinil (Provigil®) is also used in the treatment of Alzheimer's disease.

The present invention also encompasses the use of one or more compounds of formula (I) that selectively inhibit the reuptake of norepinephrine over serotonin and dopamine in combination with one or more conventional Parkinson's agents for the treatment of cognitive dysfunction in Parkinson's disease. The invention also provides a pharmaceutical composition which comprises a first component that is a conventional Parkinson's agent and a second component that is a compound of formula (I) that selectively inhibits the reuptake of norepinephrine over serotonin and dopamine. Conventional Parkinson's agents include levodopa; levodopa/carbidopa (Sinemet®); Stalevo (carbidopa/levodopa/entacapone); dopamine agonists, e.g., bromocriptine; pergolide; Mirapex® (pramipexole), Permax® (pergolide), and Requip® (ropinirole); COMT inhibitors, e.g., tolcapone, and entacapone; Selegiline (Deprenyl®; Eldepryl®); propranolol; primidone; anticholinergics, e.g., Cogentin®, Artane®, Akineton®, Disipal®, and Kemadrin®; and amantadine.

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In each of the combination treatments mentioned above, said first and second components may be administered simultaneously, separately or sequentially. Similarly, said compositions encompass combined preparations for simultaneous, separate or sequential use.

5

Another preferred group of compounds of the present invention selectively inhibit the reuptake of norepinephrine, serotonin and dopamine. Compounds of the present invention with this pharmacological profile are particularly useful for the treatment of a variety of conditions such as depression, obesity, compulsive disorders (including bulimia,

10 obsessive compulsive disorder, drug addiction including cocaine abuse and alcohol addiction), hypertension, senile dementia, Alzheimer's, memory loss, attention-deficit hyperactivity disorder (ADHD), sexual dysfunction, Parkinsonism, anxiety, chronic fatigue syndrome, panic disorders, cognitive disorders, schizophrenia, gastrointestinal disorders, headache, cardiovascular disorders, epilepsy, smoking cessation, pain including  
15 chronic pain, urinary incontinence, emesis and sleep disorders. They are most particularly useful for the treatment of depression, chronic pain, smoking cessation and obesity.

Accordingly, the present invention provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof for use in therapy. In particular, the present  
20 invention provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof for use as an inhibitor of the uptake of one or more of the monoamine neurotransmitters serotonin, dopamine and norepinephrine.

In another embodiment, the present invention provides a method for inhibiting the uptake  
25 of one or more monoamines selected from serotonin, dopamine and norepinephrine in a mammal, comprising administering to a mammal in need of such inhibition an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof. In particular, the present invention provides a method for treating a disorder which is caused by or linked to decreased neurotransmission of one or more monoamines selected from  
30 serotonin, dopamine and norepinephrine in a mammal, comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula (I) or a

pharmaceutically acceptable salt thereof. Such disorders include, for example, disorders of the central and/or peripheral nervous system. Examples of disorders of the central and/or peripheral nervous system are specifically identified above.

- 5 It is recognized that the terms "treatment" and "treating" are intended to include improvement of the disorders described herein. Thus, the terms "treatment" and "treating" are intended to refer to all processes wherein there may be a slowing, interrupting, arresting, controlling, or stopping of the progression of the disorders described herein, but does not necessarily indicate a total elimination of all symptoms,
- 10 and is intended to include prophylactic treatment of such disorders.

- In another alternative embodiment, the present invention provides for the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for inhibiting the uptake of one or more monoamines
- 15 selected from serotonin, dopamine and norepinephrine. In particular, the present invention provides for the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of a disorder which is caused by or linked to decreased neurotransmission of one or more monoamines selected from serotonin, dopamine and norepinephrine. Such disorders
- 20 include, for example, disorders of the central and/or peripheral nervous system. Examples of disorders of the central and/or peripheral nervous system are specifically identified above.

- 25 The compounds may be administered by various routes and are usually employed in the form of a pharmaceutical composition.

Accordingly, in a further embodiment, the present invention provides a pharmaceutical composition comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable diluent or carrier.

Such compositions may be prepared by methods well known in the pharmaceutical art and normally comprise at least one active compound in association with a pharmaceutically acceptable diluent or carrier. In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier or diluted by a carrier,  
5 and/or enclosed within a carrier which may, for example, be in the form of a capsule, sachet, paper or other container.

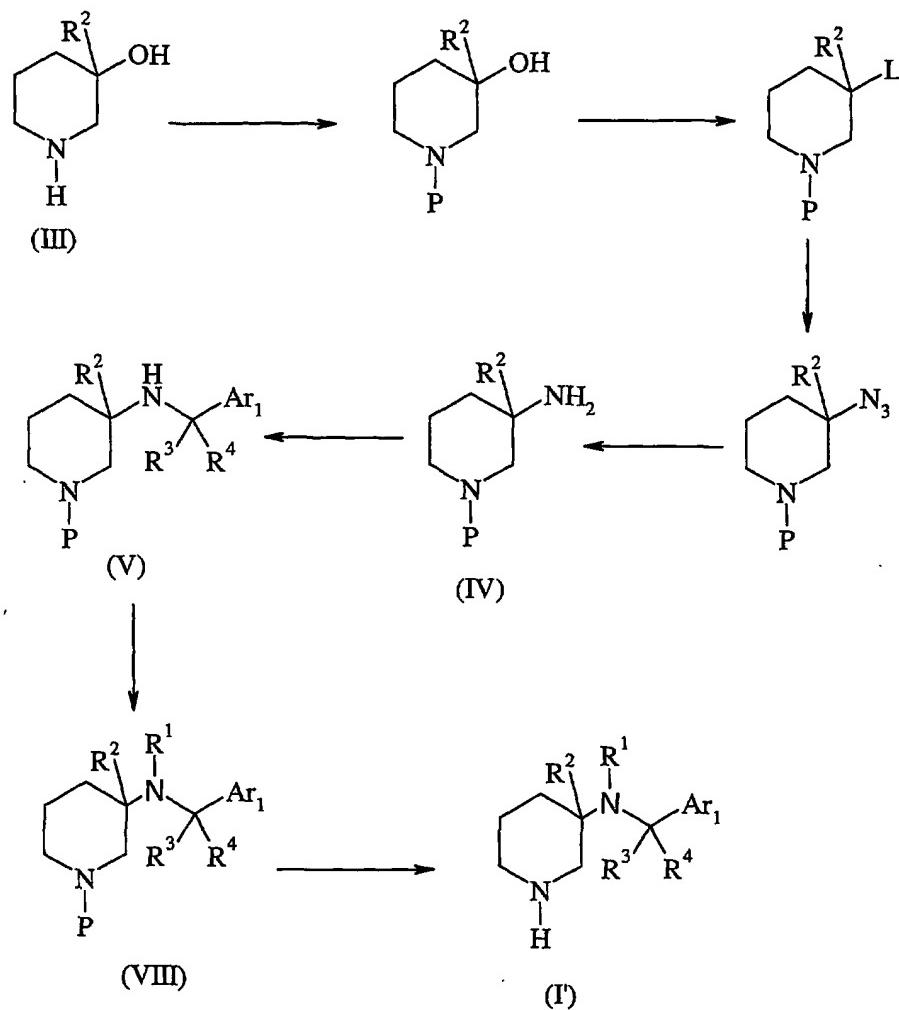
- The compositions indicated can be sterilized and/or can contain auxiliaries such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for affecting  
10 the osmotic pressure, buffer substances, colourants, flavourings and/or one or more further active compounds. Compositions of the invention may be formulated so as to provide, quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.
- 15 The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 to about 500 mg of the active ingredient.

In the context of the present specification, the term "unit dosage form" refers to physically discrete units suitable as unitary doses for human subjects and other mammals,  
20 each unit containing a predetermined quantity of one or more compounds of Formula (I) or pharmaceutically acceptable salts thereof, calculated to produce the desired therapeutic effect, together with a pharmaceutically acceptable diluent or carrier.

Compounds of formula (I) may be prepared by conventional organic chemistry  
25 techniques and also by solid phase synthesis.

Compounds of formula (I') can be prepared by the general methods illustrated below. It will be appreciated that the same methods can be used for compounds of formula (I') with the only difference that the nitrogen atom of the quinuclidines does not need to be  
30 protected as it is already a tertiary amine as it is explained in more detail below with reference to Scheme 1'.

Compounds of formula (I') can be prepared via the 3-aminopiperidine intermediate of formula (IV) as illustrated in Scheme 1 below:



5

Scheme 1

Commercially available 3-hydroxypiperidine of formula (III) wherein R<sup>2</sup> is hydrogen, can be protected using a suitable nitrogen-protecting group such as those described in T.W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, N.Y., 1991, hereafter referred to as "Greene". For example 3-R-hydroxypiperidine 10 (III) can be protected with a tert-butoxycarbonyl group, (boc). The protection reaction can be carried out for example using Boc anhydride in a suitable solvent such as for

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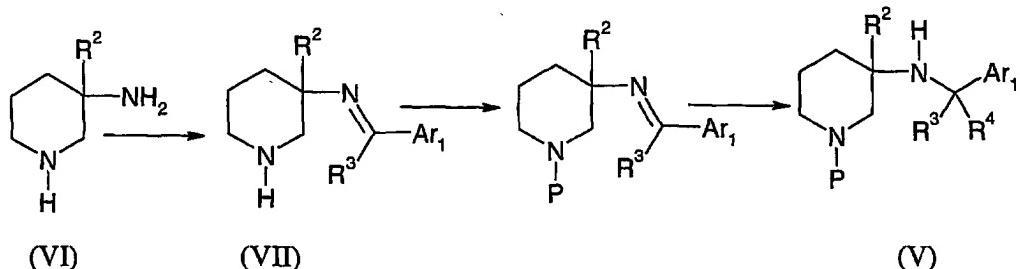
example tetrahydrofuran (THF) or dichloromethane (DCM) in the presence of a base such as triethylamine (TEA) or 4-(dimethylamino)pyridine (DMAP). It will be appreciated that for compounds of formula (I) wherein R<sup>2</sup> is C<sub>1</sub>-C<sub>2</sub> alkyl, the 3-hydroxypiperidine of formula (III) can be prepared from the readily available 3-pyrrolidinone via addition of  
5 the appropriate C<sub>1</sub>-C<sub>2</sub> alkyl organometallic.

The hydroxy group of the N-protected-3-hydroxypiperidine can be converted into a suitable leaving group (L) such as for example chloride, bromide, iodide or mesylate. For example the N-protected-hydroxypiperidine can be converted to the mesylate in the presence of mesyl chloride and a suitable base such as triethylamine in a solvent such as  
10 DCM. Said mesylate is subsequently displaced with the corresponding azide in a suitable solvent such as dimethylformamide (DMF) or dimethylsulphoxide (DMSO). This azide intermediate can be converted to the corresponding N-protected-aminopiperidine of formula (IV) via hydrogenation in the presence of a suitable catalyst such as Palladium on charcoal and in a suitable solvent such as methanol or ethanol.

15 For compounds of formula (I) wherein R<sup>4</sup> is H, intermediate (IV) can be alkylated via reductive alkylation with a ketone of formula R<sup>3</sup>-CO-Ar<sub>1</sub> wherein R<sup>3</sup> and Ar<sub>1</sub> have the values for formula (I) above. The reductive alkylation can be carried out for example as a hydrogenation reaction in the presence of a suitable catalyst such as Palladium on  
20 charcoal and a suitable solvent such as for example ethanol. Alternatively, said reductive alkylation can be carried out in the presence of a suitable borane such as sodium triacetoxyborohydride, NaBH(OAc)<sub>3</sub> and optionally in the presence of a suitable acid such as acetic acid, in a suitable solvent such as for example dichoroethane (DCE).

25 Alternatively, intermediate of formula (V) wherein R<sup>4</sup> is H can be prepared as shown in Scheme 2 below by reductive alkylation of readily available 3-aminopiperidine of formula (VI) wherein R<sup>2</sup> has the values defined for formula (I) above, followed by the protection of the nitrogen in the piperidine ring using a suitable protecting group such as those defined in Greene.

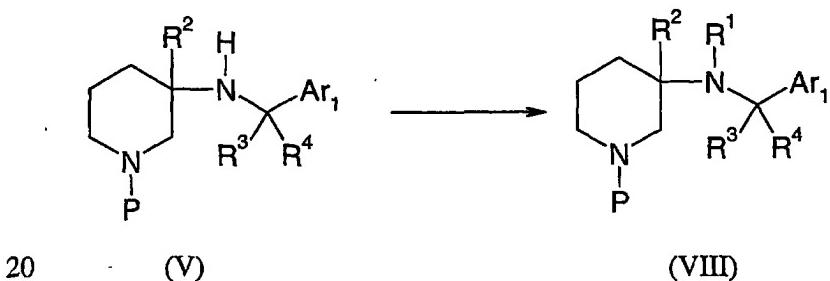
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Scheme 2

For example the reductive alkylation can be carried out in the presence of a ketone of formula Ar<sub>1</sub>-CO-R<sup>3</sup> wherein Ar<sub>1</sub> and R<sup>3</sup> have the values defined for formula (I) above. Initial condensation of the amino piperidine with the ketone is undertaken in the presence of a suitable acid such as p-toluenesulphonic acid, in a suitable solvent such as toluene. The resultant imino piperidine intermediate can then be protected with for example a boc group. The reaction can be carried out in the presence of boc anhydride and a suitable base such as DMAP, in a suitable solvent such as DCM. Said imine is reduced via hydrogenation in the presence of a suitable catalyst such as palladium on charcoal, in a suitable solvent such as ethanol to give the corresponding amine of formula (V).

Intermediate of formula (V) can be converted to compounds of formula (VIII) via  
15 reductive alkylation with an aldehyde of formula  $R^9\text{-CHO}$ , wherein  $R^9$  is chosen such that  
 $R^9\text{-CH}_2 = R^1$  and  $R^1$  has the values defined for formula (I) above. The reductive  
alkylation can be carried out using standard methods, for instance as those mentioned  
above with the ketone  $\text{Ar}_1\text{-CO-R}^3$ .

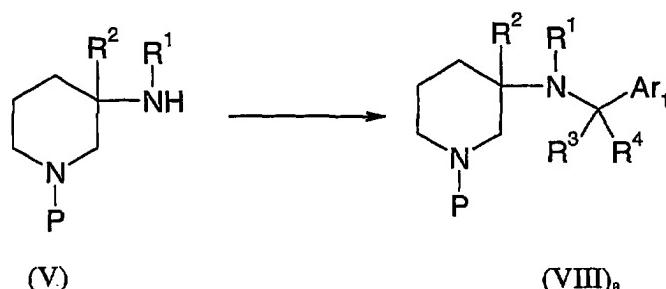


**Scheme 3**

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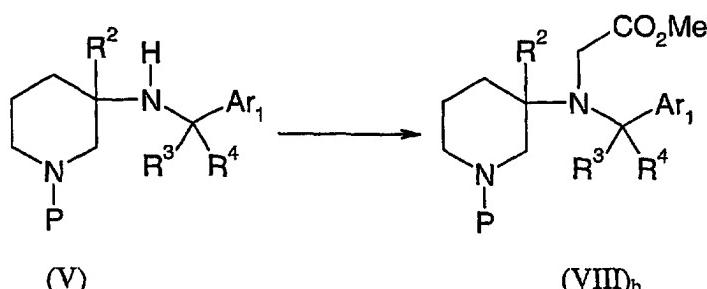
For example a compound of formula (V) can be alkylated with  $R^9\text{-CHO}$  in the presence of a suitable borane, such as  $\text{NaBH}(\text{OAc})_3$ , optionally in the presence of an acid such as acetic acid, in the presence of a suitable solvent such as dichloroethane (DCE).

- 5 For compounds of formula (I) wherein R<sup>3</sup> and R<sup>4</sup> are hydrogen the alkylation of intermediate (V) can be carried out with a compound of formula Ar<sub>1</sub>CH<sub>2</sub>L<sub>1</sub> wherein L<sub>1</sub> is a suitable leaving group such as chloro, bromo, iodo or mesylate, in the presence of a suitable base such as potassium carbonate and a suitable solvent such as acetonitrile, to give the corresponding intermediate of formula (VIII)<sub>a</sub>. It will be appreciated that the  
 10 same reaction can be carried out using Ar<sub>1</sub>-CR<sup>3</sup>R<sup>4</sup>-L<sub>1</sub> wherein R<sup>3</sup> and R<sup>4</sup> are C<sub>1</sub>-C<sub>2</sub> alkyl.



Scheme 4

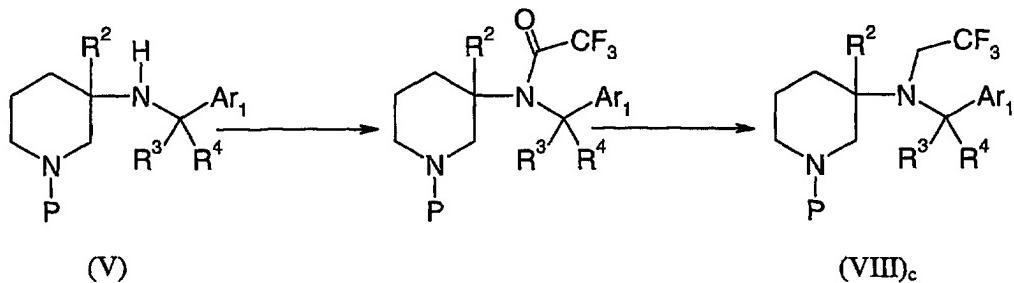
- Compounds of formula (I) wherein R<sup>1</sup> is -CH<sub>2</sub>-COO-(C<sub>1</sub>-C<sub>2</sub> alkyl) can be prepared by reacting intermediate (V) with a compound of formula L<sub>2</sub>-CH<sub>2</sub>-COO-(C<sub>1</sub>-C<sub>2</sub> alkyl) wherein L<sub>2</sub> is a suitable leaving group such as for example bromo, chloro or iodo. Said reaction can be carried out in the presence of a suitable base such as sodium hydride, in a suitable solvent such as dimethylformamide.



Scheme 5

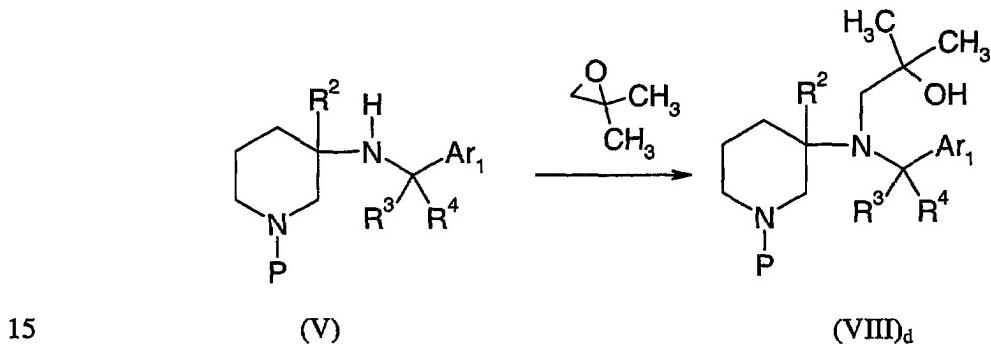
Compounds of formula (I) wherein R<sup>1</sup> is -(CH<sub>2</sub>)<sub>m</sub>-CF<sub>3</sub> can be prepared by reacting intermediate (V) with a compound of formula HOOC-(CH<sub>2</sub>)<sub>(m-1)</sub>-CF<sub>3</sub>. The acid may be

activated as its anhydride or acyl chloride, and is reacted in the presence of a suitable base such as triethylamine and a catalytic amount of DMAP, in a suitable solvent such as DCM. The resulting amide can be reduced to the amine of formula (VIII)<sub>c</sub> in the presence of a suitable borane. For example, for compounds wherein m is 1, the reduction can be carried out in the presence of  $\text{BH}_3\text{-Me}_2\text{S}$  borane-dimethyl sulphide complex, in a suitable solvent such as THF.



### Scheme 6

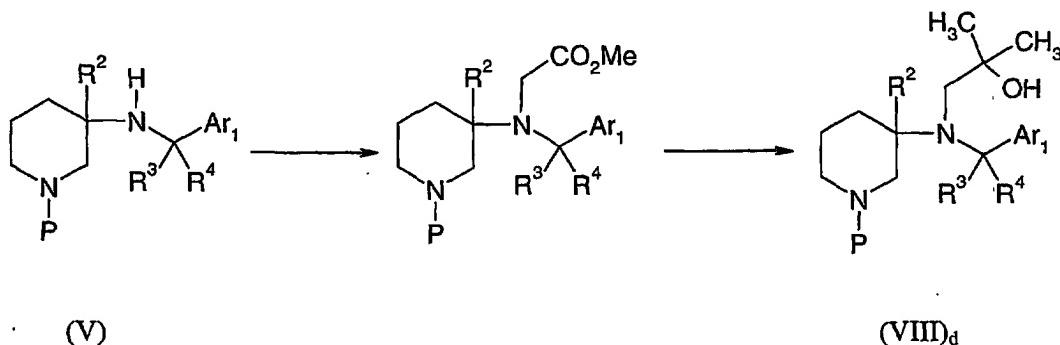
- 10 Compounds of formula (I) wherein R<sup>1</sup> is -(C<sub>1</sub>-C<sub>6</sub> alkylene)-OH can be prepared by reacting intermediate (V) with an epoxide. For example for compounds wherein R<sup>1</sup> is -CH<sub>2</sub>-C(CH<sub>3</sub>)<sub>2</sub>-OH, the intermediate of formula (V) is reacted with 2,2-dimethyloxirane, in a suitable solvent such as aqueous ethanol.



**Scheme 7**

Alternatively compounds of formula (I) wherein R<sup>1</sup> is -(C<sub>1</sub>-C<sub>6</sub>alkylene)-OH can be prepared by reacting intermediate (V) with an  $\omega$ -haloalkanoate, such as methylbromoacetate, in the presence of a base such a sodium hydrogen carbonate in a solvent such as acetonitrile. The intermediate ester is then reacted with 2 equivalents of methyl magnesium bromide in THF to yield the tertiary alcohol(VIII)<sub>d</sub>:

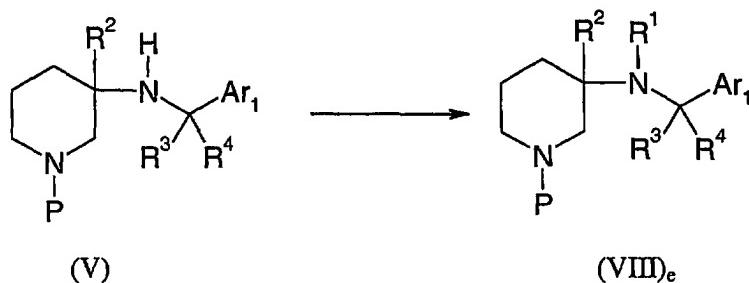
-44-



**Scheme 8**

- 5 It will be appreciated that the Scheme 8 above applies to alkylene chains longer than  
-CH<sub>2</sub>-.

Compounds of formula (I) wherein R<sup>1</sup> is -C<sub>2</sub>-C<sub>6</sub> alkenyl, -(CH<sub>2</sub>)<sub>n</sub>-S-(C<sub>1</sub>-C<sub>3</sub> alkyl), -(C<sub>1</sub>-C<sub>5</sub> alkylene)-O-(C<sub>1</sub>-C<sub>3</sub> alkyl), -(C<sub>1</sub>-C<sub>5</sub> alkylene)-O-(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), -(C<sub>1</sub>-C<sub>5</sub> alkylene)-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>3</sub> alkyl), -(C<sub>1</sub>-C<sub>5</sub> alkylene)-OCF<sub>3</sub>, or -(C<sub>1</sub>-C<sub>5</sub> alkylene)-CN, can be prepared via alkylation of intermediate (V) with a compound of formula L<sub>2</sub>-C<sub>2</sub>-C<sub>6</sub> alkenyl, L<sub>2</sub>-(CH<sub>2</sub>)<sub>n</sub>-S-(C<sub>1</sub>-C<sub>3</sub> alkyl), L<sub>2</sub>-(C<sub>1</sub>-C<sub>5</sub> alkylene)-O-(C<sub>1</sub>-C<sub>3</sub> alkyl), L<sub>2</sub>-(C<sub>1</sub>-C<sub>5</sub> alkylene)-O-(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), L<sub>2</sub>-(C<sub>1</sub>-C<sub>5</sub> alkylene)-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>3</sub> alkyl), L<sub>2</sub>-(C<sub>1</sub>-C<sub>5</sub> alkylene)-OCF<sub>3</sub>, or L<sub>2</sub>-(C<sub>1</sub>-C<sub>5</sub> alkylene)-CN respectively, wherein L<sub>2</sub> is a suitable leaving group such as chloro, bromo, iodo or mesylate, in the presence of a suitable base such as potassium carbonate and a suitable solvent such as acetonitrile, to give the corresponding intermediate of formula (VIII)<sub>e</sub>.



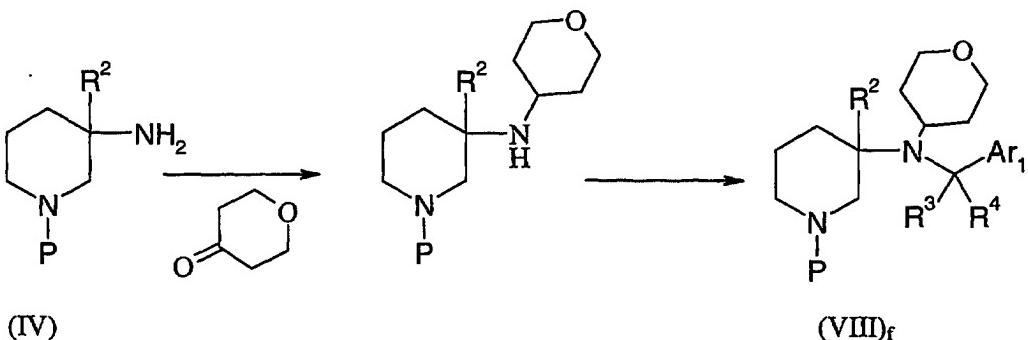
### Scheme 9

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Compounds of formula (I) wherein R<sup>1</sup> is a group of formula (i) can be prepared using the synthesis illustrated in Scheme 10 for compounds wherein R<sup>1</sup> is 4-tetrahydropyranyl. The compound of formula (IV) can be alkylated via reductive alkylation using standard

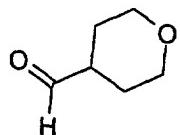
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methods, as those mentioned above with the ketone  $\text{Ar}_1\text{-CO-R}^3$ . For example a compound of formula (IV) can be alkylated with 4-tetrahydropyranone in the presence of a suitable borane, such as sodium borohydride or  $\text{NaBH(OAc)}_3$ , optionally in the presence of an acid such as acetic acid, in the presence of a suitable solvent such as dichloroethane (DCE). Then, the secondary amine can be alkylated with a compound of formula  $\text{Ar}_1\text{CH}_2\text{L}_1$  wherein  $\text{L}_1$  is a suitable leaving group such as chloro, bromo, iodo or mesylate, in the presence of a suitable base such as potassium carbonate and a suitable solvent such as acetonitrile, to give the corresponding intermediate of formula (VIII)<sub>f</sub>. It will be appreciated that as mentioned above the same reaction can be carried out using  $\text{Ar}_1\text{-CR}^3\text{R}^4\text{-L}_1$  wherein  $\text{R}^3$  and  $\text{R}^4$  are  $\text{C}_1\text{-C}_2$  alkyl.



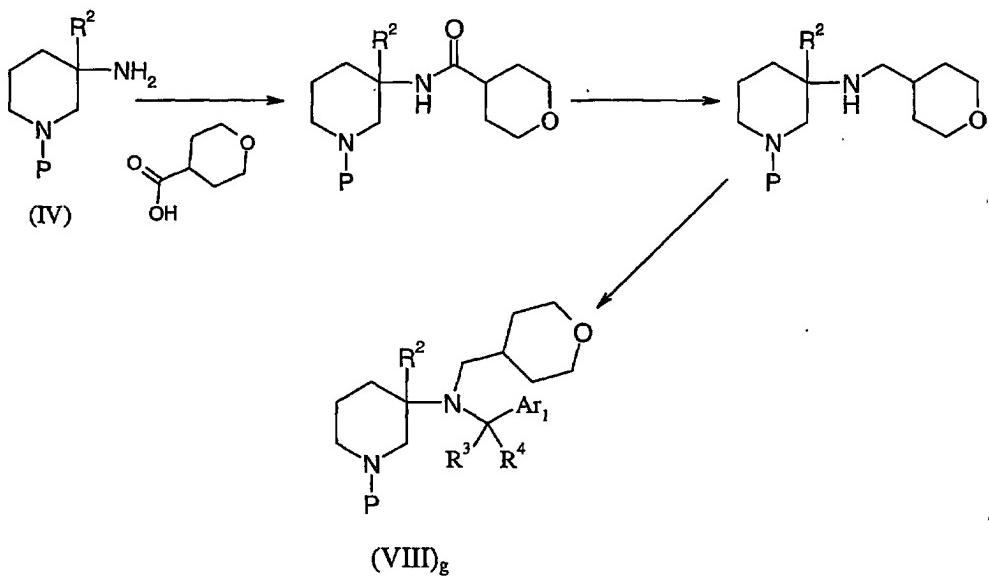
**Scheme 10**

It will be appreciated that for compounds of formula (I) wherein  $R^1$  is a group of formula (i) and r is 1 then the reductive amination can be carried out using the same reaction conditions but using the corresponding homologous aldehyde of formula



instead of the corresponding 4-tetrahydropyranone. Alternatively, compounds of formula (I) wherein R<sup>1</sup> is a group of formula (i) and r is 1 can be prepared via formation of an amide, followed by reduction of this amide bond to the corresponding amine as shown in Scheme 11 below:

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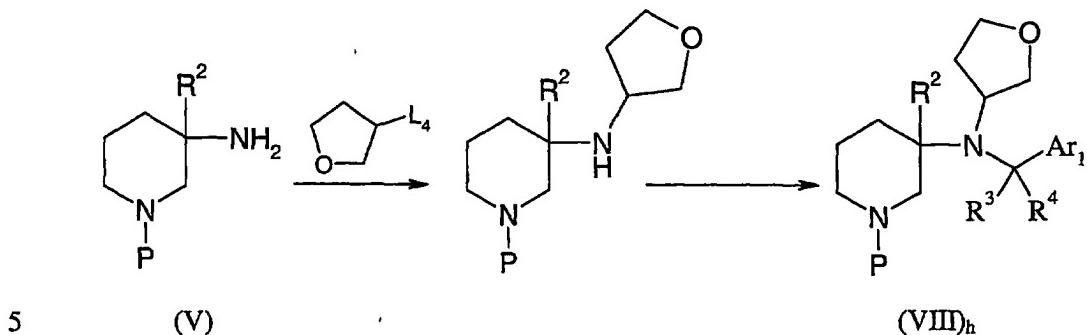


Scheme 11

- The coupling reaction can be carried out using standard methods known in the art. The  
 5 reduction of the amide bond can also be carried out by general methods known in the art for example using the same reduction conditions as those used in Scheme 6, such as in the presence of  $\text{BH}_3\text{-Me}_2\text{S}$  (borane-dimethyl sulphide complex), in a suitable solvent such as THF.
- 10 Alternatively, compounds of formula (I) wherein  $\text{R}^1$  is a group of formula (i) wherein r is 0 can be prepared by a process illustrated in Scheme 12 for compounds wherein  $-\text{Z}$  is hydrogen, s is 1, t is 2, each  $\text{R}^5$ ,  $\text{R}^6$ ,  $\text{R}^7$  and  $\text{R}^8$  are hydrogen and  $-\text{X}-$  is  $-\text{O}-$ , (i.e.  $\text{R}^1$  is tetrahydrofuran-3-yl). The compound of formula (IV) can be alkylated with a compound of formula:
- 15
- 
- wherein  $\text{L}_4$  is a suitable leaving group such as chloro, bromo, iodo, mesylate or tosylate, in the presence of a suitable base such as potassium carbonate and a suitable solvent such as acetonitrile, to give the corresponding secondary amine which can be subsequently alkylated with a compound of formula  $\text{Ar}_1\text{CH}_2\text{L}_1$  wherein  $\text{L}_1$  is a suitable leaving group such as chloro, bromo, iodo or mesylate, in the presence of a suitable base such as
- 20

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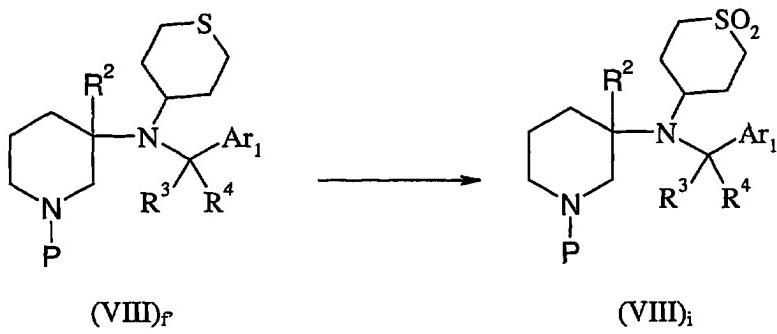
potassium carbonate and a suitable solvent such as acetonitrile, to give the corresponding intermediate of formula (VIII)<sub>f</sub>. It will be appreciated that as mentioned above the same reaction can be carried out using Ar<sub>1</sub>-CR<sup>3</sup>R<sup>4</sup>-L<sub>1</sub> wherein R<sup>3</sup> and R<sup>4</sup> are C<sub>1</sub>-C<sub>2</sub> alkyl.



Scheme 12

The tetrahydrofuryl intermediates can be prepared from the corresponding 3-hydroxytetrahydrofuran, wherein the hydroxy group is converted into the leaving group using standard methods.

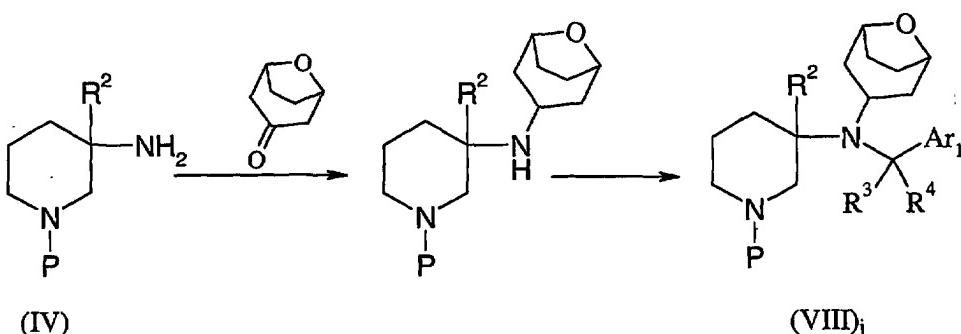
- 10 Compounds of formula (I) wherein R<sup>1</sup> is a group of formula (i) and -X- is -SO<sub>2</sub>- can be prepared from the corresponding intermediates (VIII)<sub>F</sub> wherein the thioether is oxidized to the corresponding sulphoxide as shown in Scheme 13 below:



15 Scheme 13

Compounds of formula (I) wherein R<sup>1</sup> is a group of formula (ii) can be prepared using the synthesis illustrated in Scheme 14 for compounds wherein R<sup>1</sup> is oxabicyclo[3.2.1]octan-3-yl. The compound of formula (IV) can be alkylated via reductive alkylation using standard methods, as those mentioned above with the ketone Ar<sub>1</sub>-CO-R<sup>3</sup>. For example compound of formula (IV) can be alkylated with oxabicyclo[3.2.1]octan-3-one in the presence of a suitable borane, such as sodium borohydride or NaBH(OAc)<sub>3</sub>, optionally in

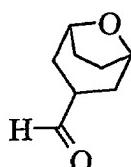
the presence of an acid such as acetic acid, in the presence of a suitable solvent such as dichloroethane (DCE). Then, the secondary amine can be alkylated with a compound of formula  $\text{Ar}_1\text{CH}_2\text{L}_1$  wherein  $\text{L}_1$  is a suitable leaving group such as chloro, bromo, iodo or mesylate, in the presence of a suitable base such as potassium carbonate and a suitable solvent such as acetonitrile, to give the corresponding intermediate of formula (VIII). It will be appreciated that as mentioned above the same reaction can be carried out using  $\text{Ar}_1\text{-CR}^3\text{R}^4\text{-L}_1$  wherein  $\text{R}^3$  and  $\text{R}^4$  are  $\text{C}_1\text{-C}_2$  alkyl.



### Scheme 14

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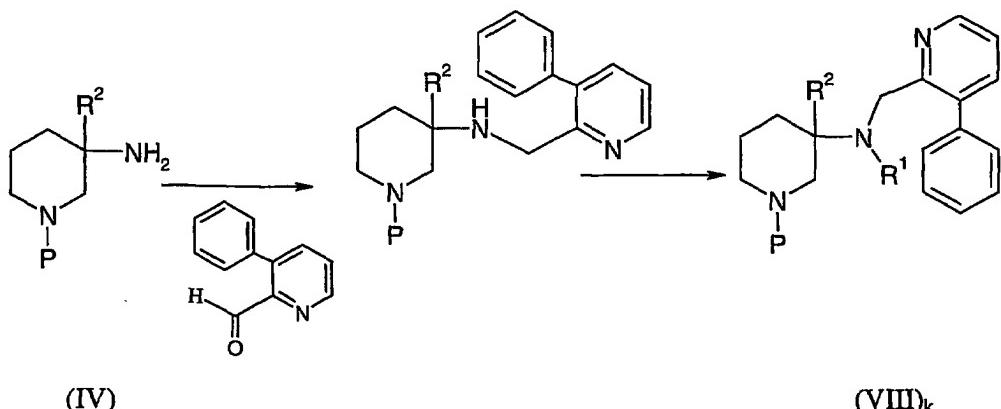
The oxabicyclo[3.2.1]octan-3-one intermediate is prepared according to the method described in A E Hill, G Greenwood and H M R Hoffmann JACS 1973, 95, 1338. It will be appreciated that for compounds of formula (I) wherein  $R^1$  is a group of formula (i) and r is 1 then the reductive amination can be carried out using the same reaction conditions but using the corresponding homologous aldehyde of formula



instead of the corresponding oxabicyclo[3.2.1]octan-3-one.

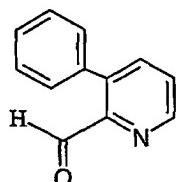
Compounds of formula (I) wherein Ar<sub>1</sub> is a substituted or unsubstituted pyridyl group can be prepared by a process illustrated in Scheme 15 for compounds wherein R<sup>3</sup> and R<sup>4</sup> are hydrogen and Ar<sub>1</sub> is 3-phenylpyrid-2-yl.

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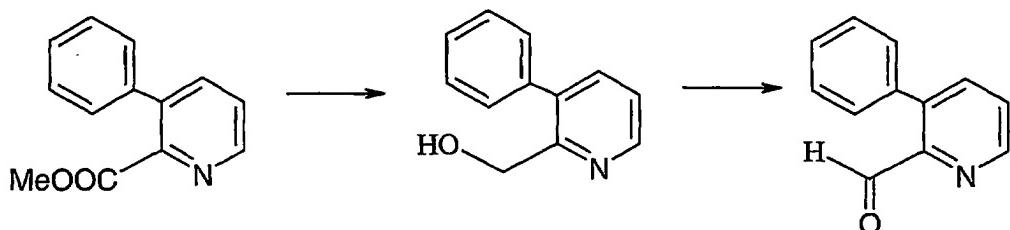


Scheme 15

The compound of formula (IV) can be alkylated via reductive alkylation using standard methods, as those mentioned above with the ketone  $\text{Ar}_1\text{-CO-R}^3$ . For example compound of formula (IV) can be alkylated with an aldehyde of formula:



in the presence of a suitable borane, such as sodium borohydride or  $\text{NaBH}(\text{OAc})_3$ , optionally in the presence of an acid such as acetic acid, in the presence of a suitable solvent such as dichloroethane (DCE). Then, the secondary amine can be alkylated using the general methods described above for the incorporation of  $\text{R}^1$ . The intermediate aldehyde can be prepared via reduction of readily available methyl 3-phenyl picolinate to the corresponding alcohol and subsequent oxidation to the aldehyde as shown in Scheme 16 below.



15

### Scheme 16

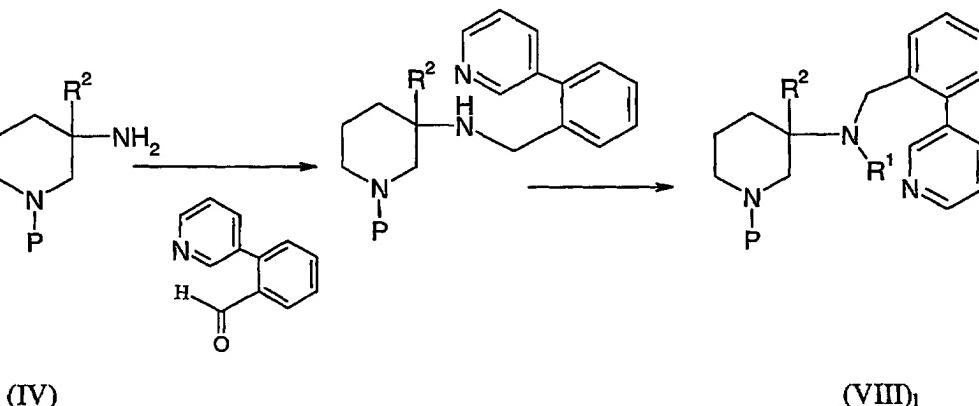
-50-

The reduction step can be carried out in the presence of a suitable reducing agent such as lithium borohydride in a suitable solvent such as tetrahydrofuran. The oxidation to the aldehyde can be carried out under Swern conditions such as oxalyl chloride and DMSO in DCM.

5

Compounds of formula (I) wherein Ar<sub>1</sub> is a substituted or unsubstituted phenyl group can be prepared by a process illustrated in Scheme 17 for compounds wherein R<sup>3</sup> and R<sup>4</sup> are hydrogen and Ar<sub>1</sub> is 2-(3-pyridyl)phenyl.

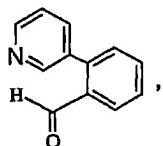
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Scheme 17

The compound of formula (IV) can be alkylated via reductive alkylation using standard methods, as those mentioned above with the ketone Ar<sub>1</sub>-CO-R<sup>3</sup>. For example compound of formula (IV) can be alkylated with an aldehyde of formula:

15

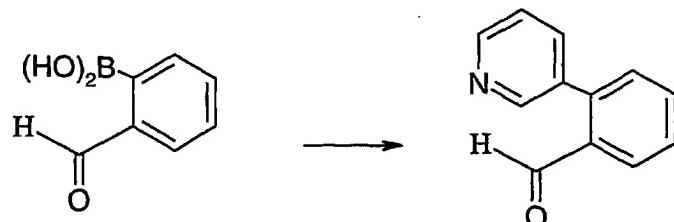


20

in the presence of a suitable borane, such as sodium borohydride or NaBH(OAc)<sub>3</sub>, optionally in the presence of an acid such as acetic acid, in the presence of a suitable solvent such as dichloroethane (DCE). Then, the secondary amine can be alkylated using the general methods described above for the incorporation of R<sup>1</sup>. The intermediate aldehyde can be prepared from the commercially available 2-formyl phenyl boronic acid via palladium coupling in the presence of 3-bromopyridine, a suitable palladium catalyst

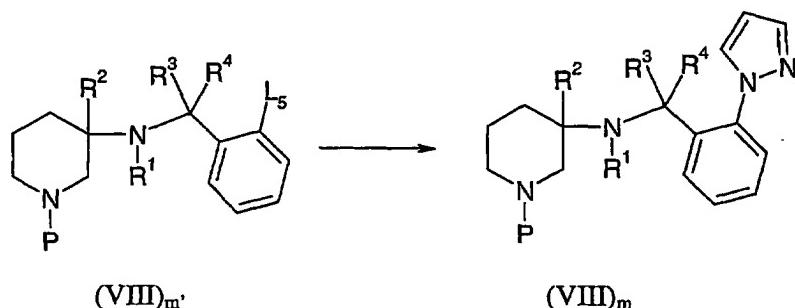
-51-

such as  $\text{Pd}(\text{PPh}_3)_4$  and a suitable base such as potassium carbonate in a suitable solvent such as acetonitrile, as shown in Scheme 18 below.



Scheme 18

- 5 Compounds of formula (I) wherein Ar<sub>1</sub> is a phenyl group substituted with a 1-pyrazole group can be prepared by a process illustrated in Scheme 19.

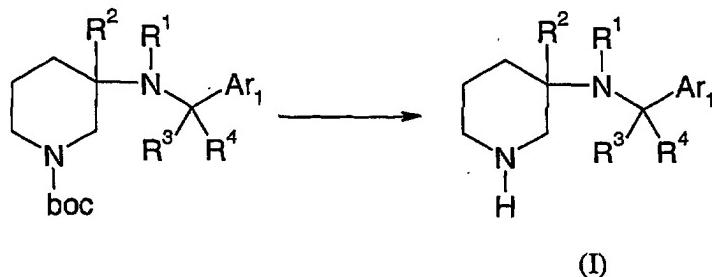


Scheme 19

- 10 The pyrazole group can be incorporated by reacting a compound of formula (VIII)<sub>m'</sub>, wherein L<sub>5</sub> is a suitable leaving group such as bromo, chloro or iodo, with pyrazole in the presence of a suitable base such as potassium carbonate and a catalytic amount of copper iodide in a suitable solvent such as for example DMF. The compound of formula (VIII)<sub>m'</sub> can be prepared by any of the methods mentioned above for compounds wherein Ar1 is a phenyl group substituted with a halogen atom such as chloro, bromo or iodo.
- 15

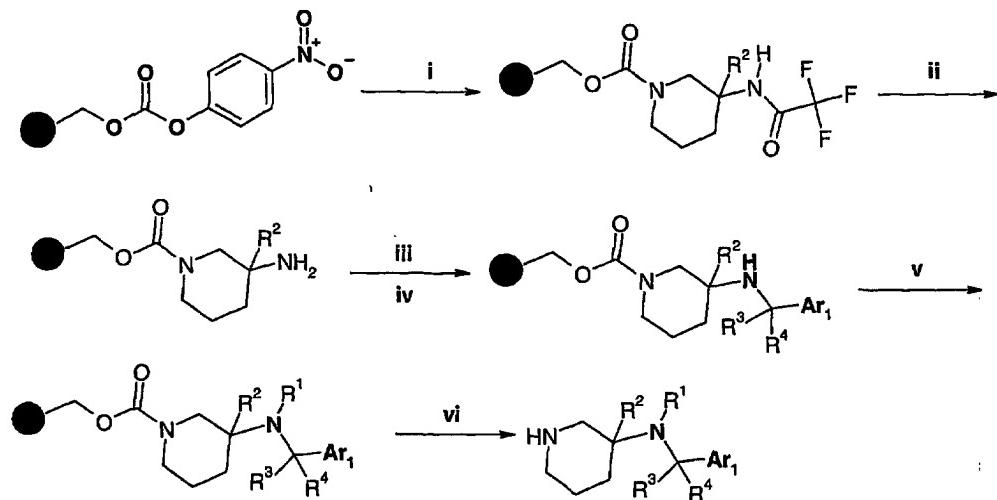
- It will be appreciated that any of the intermediates (VIII), (VIII)<sub>a-m</sub> are then deprotected using suitable deprotecting conditions such as those discussed in Greene, to give the corresponding compounds of formula (I). For example if the protecting group is a boc group, the deprotection reaction can be carried out in trifluoroacetic acid in a suitable solvent such as DCM. Alternatively the reaction can be carried out in ethanolic hydrochloric acid.
- 20

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Scheme 20

Compounds of formula (I) wherein *R*<sup>3</sup> and *R*<sup>4</sup> are both hydrogen may also be prepared by  
5 solid phase synthesis by the route shown below.

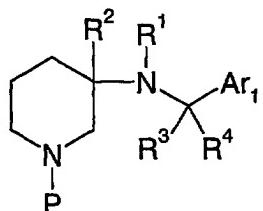


The sequence is preferably performed on a polystyrene resin. The process may be run in a combinatorial fashion such that all possible compounds from sets of precursors Ar<sub>1</sub>CHO and R<sup>9</sup>CHO may be prepared, wherein R<sup>9</sup> is chosen such that R<sup>9</sup>-CH<sub>2</sub> = R<sup>1</sup>, and R<sup>1</sup> and  
10 Ar<sub>1</sub> have the values defined above for formula (I). The sequence is performed without characterisation of the resin-bound intermediates. In step (i) 3-trifluoroacetamido-piperidine is bound to a solid support by reaction with 4-nitrophenyl carbonate activated polystyrene resin in the presence of a base, such as N,N-diisopropylethylamine, in a solvent such as DMF. In step (ii), the trifluoroacetamido protecting group is cleaved by hydrolysis with a base such as aqueous lithium hydroxide. In step (iii) the primary amine is then condensed with a substituted benzaldehyde in the presence of a dehydrating agent, such as trimethylorthoformate, to form the intermediate imine. In step (iv) the imine is reduced with a borane reducing agent, such as sodium cyanoborohydride, in a solvent  
15

such as DMF, containing acetic acid. In step (v) the resultant secondary amine is then reductively alkylated with an aldehyde in the presence of a reducing agent such as sodium triacetoxyborohydride in a solvent, such as DMF. In step (vi) the desired product is finally cleaved from the resin with acid, such as aqueous trifluoroacetic acid.

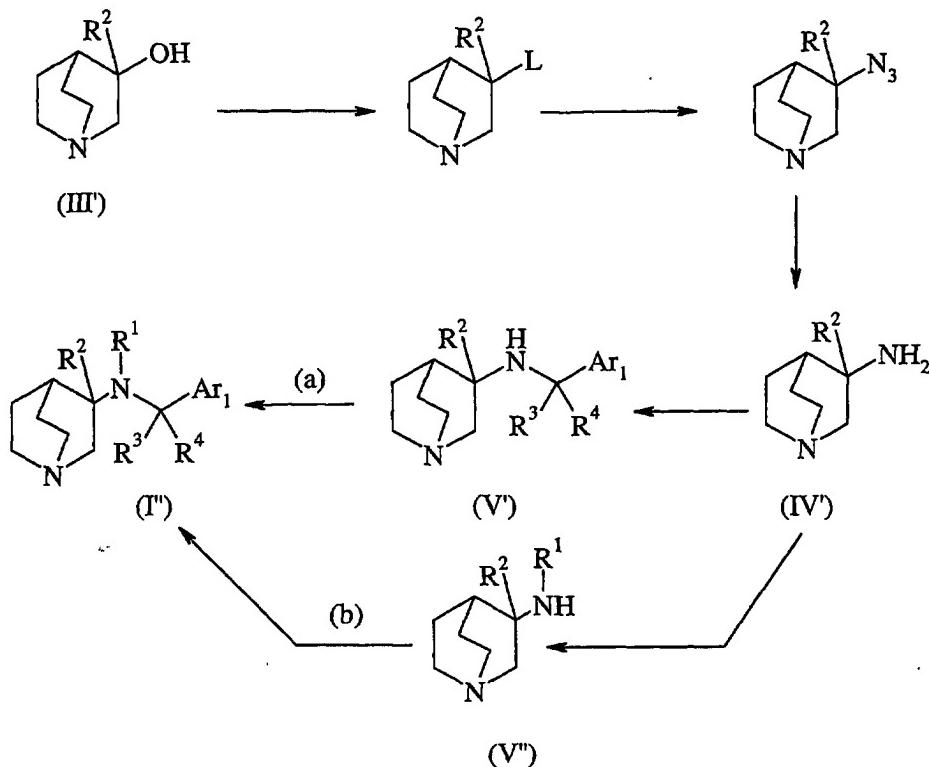
5

The present invention also provides a process for producing a compound of formula (I') above, which comprises deprotecting a compound of the formula (VIII)



- 10 where P is an N-protecting group, optionally followed by the further step of forming a pharmaceutically acceptable salt. Suitable N-protecting groups will be known to the person skilled in the art and are described in, for example, Greene. They include, for example, boc, benzyl, benzyloxycarbonyl and acetyl.
- 15 As mentioned above, compounds of formula (I'') can be prepared via the 3-aminoquinuclidine intermediate of formula (IV') using the same methods as for the 3-aminopiperidine intermediate of formula (IV). It is further illustrated in the Scheme 1' below, wherein as explained above the quinuclidine does not need to be protected:

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Scheme 1'

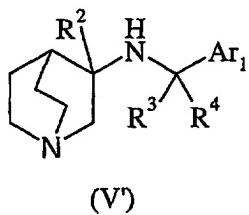
Intermediate of formula (IV') wherein R<sup>2</sup> is hydrogen, 3-aminoquinuclidine, is commercially available. For compounds of formula (I'') wherein R<sup>2</sup> is C<sub>1</sub>-C<sub>2</sub> alkyl, the 3-hydroxyquinuclidine of formula (III') can be prepared from the commercially available 3-quinuclidinone via addition of the appropriate C<sub>1</sub>-C<sub>2</sub> alkyl organometallic. Then, the hydroxy group can be converted into a suitable leaving group (L) such as for example chloride, bromide, iodide or mesylate as illustrated in Scheme 1 above, via the methods mentioned above for the piperidine derivatives.

10

The present invention also provides a process for producing a compound of formula (I'') above, which comprises either

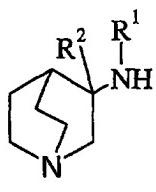
- (a) reacting a compound of the formula (V')

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with an aldehyde of formula  $R^9\text{-CHO}$ , wherein  $R^9$  is chosen such that  $R^9\text{-CH}_2 = R^1$  and  $R^1$  has the values defined for formula (I) above, in the presence of a suitable reducing agent, or

5 (b) reacting a compound of formula



with

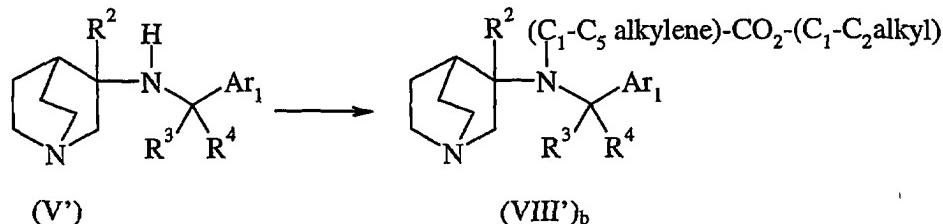
- (i) a compound of formula  $\text{Ar}_1\text{-CR}^3\text{R}^4\text{-L}_1$  wherein  $\text{Ar}_1$ ,  $R^3$  and  $R^4$  have the values defined for formula (I) above and  $L_1$  is a suitable leaving group such as chloro, bromo, iodo or mesylate, in the presence of a suitable base, or
- (ii) a compound of formula  $\text{Ar}_1\text{-CO-}R^3$ , wherein  $\text{Ar}_1$ , and  $R^3$  have the values defined for formula (I) above, in the presence of a suitable reducing agent.

The following synthetic methods illustrate further processes for the preparation of a compound of formula (I'') above. It will be understood that the reagents used in each synthetic method are those mentioned above for the schemes with the same number. It 20 will be appreciated that the last step of each synthesis also represent further aspects of the present invention. Compounds of formula (I'') wherein:

- (i)  $R^1$  is  $-(C_1\text{-}C_5 \text{ alkylene})\text{-CO}_2\text{-(C}_1\text{-C}_2 \text{ alkyl)}$  can be prepared by reacting intermediate (V) with a compound of formula  $L_2\text{-(C}_1\text{-C}_5 \text{ alkylene)-CO}_2\text{-(C}_1\text{-C}_2$

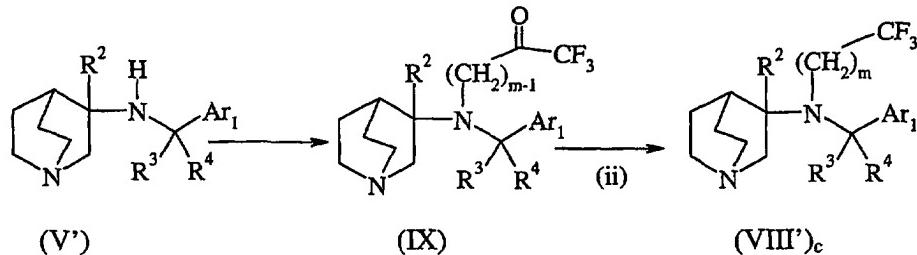
-56-

alkyl) wherein L<sub>2</sub> is a suitable leaving group such as for example bromo, chloro or iodo:



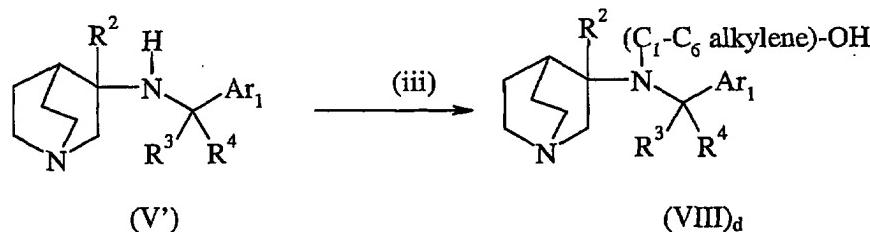
### 5 Scheme 5'

(ii) R<sup>1</sup> is -(CH<sub>2</sub>)<sub>m</sub>-CF<sub>3</sub> can be prepared by reducing an amide intermediate (IX) with a suitable reducing agent;



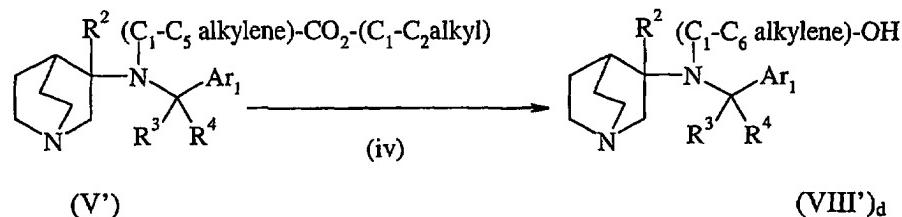
10 Scheme 6'

(iii) R<sup>1</sup> is -(C<sub>1</sub>-C<sub>6</sub> alkylene)-OH can be prepared by reacting intermediate (V') with a suitable epoxide;



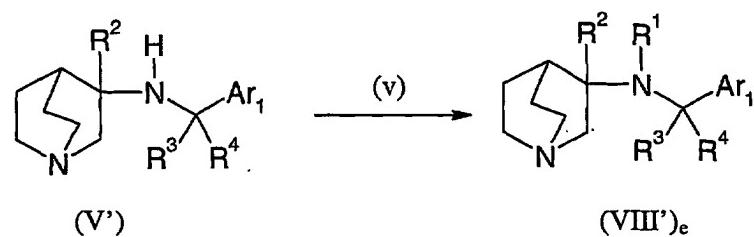
15 Scheme 7'

(iv) R<sup>1</sup> is -(C<sub>1</sub>-C<sub>6</sub> alkylene)-OH can be prepared by reacting intermediate (V') with suitable organometallic compounds;



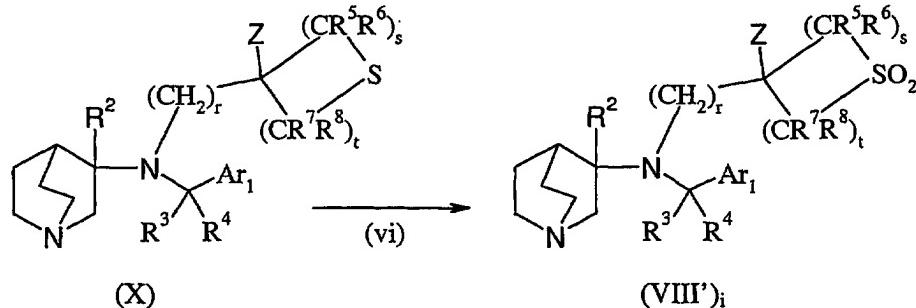
Scheme 8'

(v) R<sup>1</sup> is -C<sub>2</sub>-C<sub>6</sub> alkenyl, -(CH<sub>2</sub>)<sub>n</sub>-S-(C<sub>1</sub>-C<sub>3</sub> alkyl), -(C<sub>1</sub>-C<sub>5</sub> alkylene)-O-(C<sub>1</sub>-C<sub>3</sub> alkyl), -(C<sub>1</sub>-C<sub>5</sub> alkylene)-O-(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), -(C<sub>1</sub>-C<sub>5</sub> alkylene)-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>3</sub> alkyl), -(C<sub>1</sub>-C<sub>5</sub> alkylene)-OCF<sub>3</sub>, or -(C<sub>1</sub>-C<sub>5</sub> alkylene)-CN, can be prepared via alkylation of intermediate (V') with a compound of formula L<sub>2</sub>-C<sub>2</sub>-C<sub>6</sub> alkenyl, L<sub>2</sub>-(CH<sub>2</sub>)<sub>n</sub>-S-(C<sub>1</sub>-C<sub>3</sub> alkyl), L<sub>2</sub>-(C<sub>1</sub>-C<sub>5</sub> alkylene)-O-(C<sub>1</sub>-C<sub>3</sub> alkyl), L<sub>2</sub>-(C<sub>1</sub>-C<sub>5</sub> alkylene)-O-(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), L<sub>2</sub>-(C<sub>1</sub>-C<sub>5</sub> alkylene)-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>3</sub> alkyl), L<sub>2</sub>-(C<sub>1</sub>-C<sub>5</sub> alkylene)-OCF<sub>3</sub>, or L<sub>2</sub>-(C<sub>1</sub>-C<sub>5</sub> alkylene)-CN respectively, wherein L<sub>2</sub> is a suitable leaving group such as chloro, bromo, iodo or mesylate, in the presence of a suitable base;



Scheme 9'

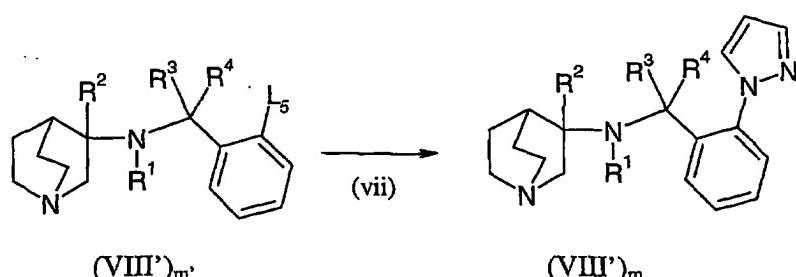
(vi) R<sup>1</sup> is a group of formula (i)-(C<sub>1</sub>-C<sub>6</sub> alkylene)-OH can be prepared by oxidising intermediate (X) with a suitable oxidising agent;



Scheme 13'

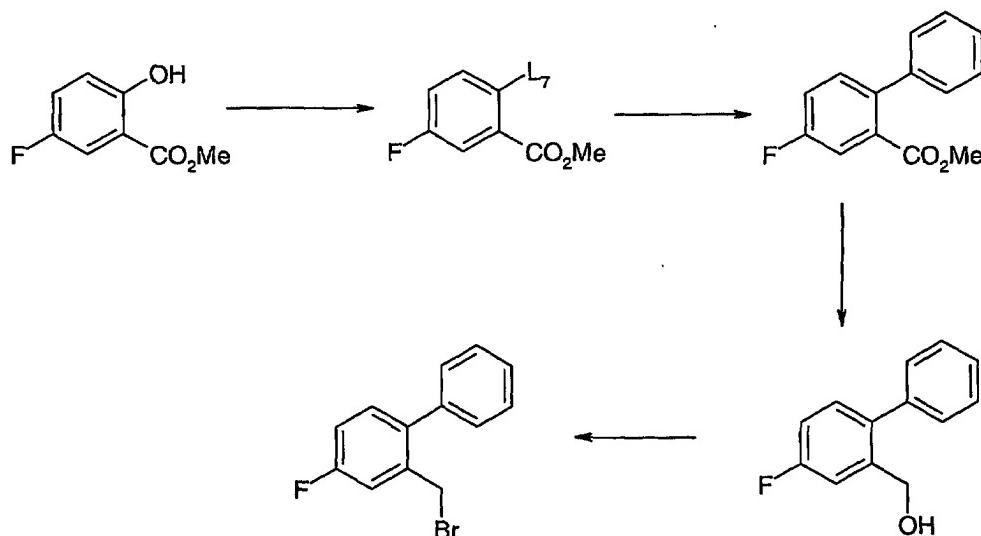
(vii) Ar<sub>1</sub> is a phenyl group substituted with a 1-pyrazole group can be prepared by reacting a compound of formula (VIII'<sub>m</sub>), wherein L<sub>5</sub> is a suitable leaving group such as bromo, chloro or iodo, with pyrazole in the presence of a suitable base;

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### Scheme 19'

It will be appreciated that certain intermediates  $\text{Ar}_1\text{CR}^3\text{R}^4\text{L}_6$ , wherein  $\text{L}_6$  is a suitable leaving group, such as for example mesylate, tosylate, bromo, chloro or iodo, used in the general methods mentioned above are not commercially available and need to be prepared according to suitable methods known in the art illustrated in the preparations and examples below. For example, the intermediate wherein  $\text{Ar}_1$  is 2-phenyl-5-fluorophenyl,  $\text{R}^3$  and  $\text{R}^4$  are hydrogen, and  $\text{L}_6$  is bromo can be prepared as illustrated in Scheme 21 below:



### Scheme 21

Methyl 5-fluorosalicylate was activated by converting the hydroxy group into a suitable leaving group L<sub>7</sub>, such as for example a triflate, by reaction with a sulfonylating reagent such as N-phenyl trifluorosulfonimide in the presence of a base such as sodium hydride in a solvent such as DMF. The triflate was then reacted with phenyl boronic acid under

palladium catalysis, using palladium acetate in the presence of tricyclohexyl phosphine and a base such as potassium fluoride in a solvent such as THF. The ester was then reduced to the benzyl alcohol with lithium aluminium hydride in a solvent such as THF. Finally the benzyl bromide was formed using a brominating agent such as 5 triphenylphosphine dibromide in a solvent such as chloroform.

The following Preparations and Examples illustrate routes to the synthesis of the compounds of the invention.

10 **Preparation 1: 1,1-Dimethylethyl (3S)-3-aminopiperidine-1-carboxylate**

a) 1,1-Dimethylethyl (3R)-3-hydroxypiperidine-1-carboxylate

Solid *d*itert-butyl dicarbonate (26.6g, 122mmol) was added in portions over 15 minutes to a stirred solution of (3*R*)-piperidin-3-ol hydrochloride (15.25g, 111mmol), triethylamine (30.9mL, 222mmol) and 4-(dimethylamino)-pyridine (50mg) in dry dichloromethane (300mL). After stirring for 18 hours at room temperature, the mixture was washed with aqueous citric acid, then brine. The organic extracts were dried (MgSO<sub>4</sub>), filtered and evaporated *in vacuo* to give an oil. This was purified by flash chromatography on silica, eluting with ethyl acetate/cyclohexane (20:80 to 80:20), to give the title compound as a solid.

20

b) 1,1-Dimethylethyl (3*R*)-3-[(methylsulfonyl)oxy]-piperidine-1-carboxylate

Methanesulfonyl chloride (9.56mL, 124mmol) was added dropwise over 10 minutes to a stirred solution of 1,1-dimethylethyl (3*R*)-3-hydroxypiperidine-1-carboxylate (20.7g, 103mmol) and triethylamine (21.5mL, 154mmol) in dichloromethane (300mL) at 0°C.

25 After stirring for 3 hour at 0°C, the reaction was quenched by addition of water. The organic phase was washed with brine, dried (MgSO<sub>4</sub>), filtered and evaporated *in vacuo* to give an oil. This was purified by flash chromatography on silica, eluting with ethyl acetate/cyclohexane (20:80 to 50:50), to give the title compound as an oil.

30 c) 1,1-Dimethylethyl (3*S*)-3-azidopiperidine-1-carboxylate

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Sodium azide (7.65g, 118mmol) was added to a solution of 1,1-dimethylethyl (3*R*)-3-[(methylsulfonyl)oxy]-piperidine-1-carboxylate (21.9g, 78.5mmol) in dry dimethylformamide (120mL) and the resultant suspension heated at 70°C for 48 hours. After cooling to room temperature, the reaction mixture was diluted with water and extracted into ethyl acetate. The organic phase was washed two further times with water, then brine. The organic extracts were dried ( $MgSO_4$ ), filtered and evaporated *in vacuo* to give an oil. This was purified by flash chromatography on silica, eluting with ethyl acetate/cyclohexane (10:90 to 50:50), to give the title compound as an oil.

5 10 d) 1,1-Dimethylethyl (3*S*)-3-aminopiperidine-1-carboxylate

A mixture of 1,1-dimethylethyl (3*S*)-3-azidopiperidine-1-carboxylate (7.5g) and 10% palladium-on-carbon (0.75g) in methanol (100mL) was hydrogenated in a Parr apparatus at 70 p.s.i. for 16 hours. The catalyst was removed by filtration through Celite and the solvent evaporated *in vacuo* to give an oil. The resultant title compound was used in 15 subsequent reactions without further purification.

Preparation 2: 2-(Bromomethyl)-4-fluoro-1,1'-biphenyl

a) Methyl 5-fluoro-2-{[(trifluoromethyl)sulfonyl]oxy}benzoate  
5-Fluorosalicylic acid methyl ester (28.2g, 166mmol) was dissolved in dry 20 dimethylformamide (165mL) and stirred as sodium hydride (60% in oil) (7.30g, 1.1eq) was added portionwise over 30 mins at 0°C. The reaction mixture was stirred for a further 30 mins at room temperature, then *N*-phenyl trifluoromethanesulfonimide (62.8g, 1.05eq) was added in portions over 30 mins, then left to stir for 3 hours. The mixture was diluted with diethyl ether and washed successively with water, then brine. The organic layers 25 were combined, dried ( $MgSO_4$ ), filtered and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography on silica, eluting with ethyl acetate/cyclohexane (10:90 to 40:60), to give the title compound as an oil.

b) Methyl 4-fluoro-[1,1'-biphenyl]-2-carboxylate  
30 Palladium acetate (635mg, 0.05eq), tricyclohexyl-phosphine (952mg, 0.06eq), potassium fluoride (10.85g, 3.3eq) and phenyl boronic acid (7.6g, 1.1eq) were taken up in

dry THF (150mL) and the reaction mixture flushed with nitrogen for 5 mins. A solution of methyl 5-fluoro-2-[(trifluoromethyl)sulfonyl]oxybenzoate (17.12g, 56.7 mmol) in THF (20mL) was added in one portion and the reaction mixture stirred at reflux under nitrogen for 5 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, then washed with water, dried ( $\text{MgSO}_4$ ), filtered and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography on silica, eluting with ethyl acetate/cyclohexane (3:97 to 10:90), to give the title compound as an oil.

c) (4-Fluoro-[1,1'-biphenyl]-2-yl)methanol

10 A solution of methyl 4-fluoro-[1,1'-biphenyl]-2-carboxylate (3g, 13.1mmol) in THF (20mL) was added at 0°C to a suspension of lithium aluminium hydride pellets (1g, 26mmol) in THF (30mL). Upon addition the reaction mixture was heated at 60°C under nitrogen for 2 h. The reaction was then cooled to 0°C and the excess lithium aluminium hydride destroyed by adding water, then 1N sodium hydroxide (2mL). The mixture was 15 extracted into diethyl ether and the organic phase was dried ( $\text{MgSO}_4$ ), filtered and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography on silica, eluting with ethyl acetate/heptane (2:98 to 25:75), to give the title compound as an oil.

20 d) 2-(Bromomethyl)-4-fluoro-1,1'-biphenyl

Triphenylphosphine dibromide (35.5g, 2eq) was added in one portion to a solution of (4-fluoro-[1,1'-biphenyl]-2-yl)methanol (8.5g, 42mmol) in chloroform (250mL). The reaction mixture was heated at 60°C and left to stir overnight. The solid was filtered off and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography 25 on silica, eluting with ethyl acetate/cyclohexane (0:100 to 30:70), to give the title compound as an oil.

Example 1: (3S)-N-(2-Methylpropyl)-N-[[2-(trifluoromethyl)-phenyl]methyl}piperidin-3-amine, fumarate

30 a) 1,1-Dimethylethyl (3S)-3-({[2-(trifluoromethyl)-phenyl]methyl}amino)piperidine-1-carboxylate

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1,1-Dimethylethyl (3*S*)-3-aminopiperidine-1-carboxylate (1.0g, 5mmol), 2-trifluoromethylbenzaldehyde (0.87g, 5mmol), 5% palladium on carbon (0.35g) and ethanol (40mL) were hydrogenated at 60psi for 2.5 h. using a Parr hydrogenator. The catalyst was filtered off and the filtrate evaporated *in vacuo*. The resultant oil was  
5 purified by flash chromatography on silica, eluting with ethyl acetate/cyclohexane (0:100 to 75:25), to give the title compound as an oil.

b) 1,1-Dimethylethyl (3*S*)-3-((2-methylpropyl){[2-(trifluoromethyl)phenyl]methyl}amino)piperidine-1-carboxylate  
10 Sodium triacetoxyborohydride (0.23g, 1.08mmol) was added to a stirred solution of 1,1-dimethylethyl (3*S*)-3-((2-(trifluoromethyl)phenyl)methyl)amino)piperidine-1-carboxylate (0.19g, 0.53mmol), isobutyraldehyde (0.12g, 1.6mmol) and 1,2-dichloroethane (5mL). After stirring under nitrogen at room temperature for 1 day, the reaction mixture was diluted with methanol (6mL) and absorbed onto a cationic ion  
15 exchange resin (Isolute™ SCX-2). After washing the cartridge with methanol (25mL), the basic components were isolated by elution with 2N ammonia in methanol and the eluate evaporated to give an oil.

c) (3*S*)-*N*-(2-Methylpropyl)-*N*-{[2-(trifluoromethyl)-phenyl]methyl}piperidin-3-amine,  
20 fumarate

1,1-Dimethylethyl (3*S*)-3-((2-methylpropyl){[2-(trifluoromethyl)phenyl]methyl}amino)piperidine-1-carboxylate (0.139mg, 0.335mmol), trifluoroacetic acid (4mL) and dichloromethane (10mL) were stirred at room temperature for 1 day. The solution was evaporated *in vacuo* to give an oil, which was redissolved in  
25 methanol and filtered through a cationic ion exchange resin (Isolute™ SCX-2). The basic components were isolated by elution with 2N ammonia in methanol. The eluate was evaporated *in vacuo* and the resultant oil converted to the fumaric acid salt (crystallisation from ethanol/ether), to give the title compound as a white solid. <sup>1</sup>H NMR (300MHz, CD<sub>3</sub>OD): δ<sub>H</sub> 7.77-7.74 (d, H), 7.51-7.43 (m, 2H), 7.25-7.22 (t, 1H), 4.23 (s, 2H), 3.79-  
30 3.66 (q, 2H), 3.21-3.08 (m, 4H), 2.83-2.61 (m, 3H), 2.28-2.10 (m, 2H), 1.90-1.82 (m, 2H), 1.59-1.37 (m, 3H), 0.77-72 (t, 6H); MS: (M+H) = 315.

The following Examples were similarly prepared as described above for Example 1, by reductive alkylation of 1,1-dimethylethyl (3S)-3-({[2-(trifluoromethyl)-  
5 phenyl]methyl}amino)piperidine-1-carboxylate with the appropriate aldehyde or ketone, and subsequent deprotection:

**Example 2: (3S)-N-(3,3-Dimethylbutyl)-N-{{[2-(trifluoromethyl)-phenyl]methyl}piperidin-3-amine, D-tartrate**

10  $^1\text{H}$ NMR (300MHz, CD<sub>3</sub>OD):  $\delta_{\text{H}}$  7.79-7.86 (d, 1H), 7.47-7.56 (m, 2H), 7.27-7.32 (t, 2H), 4.30 (s, 2H), 3.73-3.84 (t, 2H), 3.16-3.28 (m, 2H), 2.71-2.89 (m, 3H), 2.47-2.52 (t, 2H), 1.84-1.97 (m, 2H), 1.47-1.63 (m, 2H), 1.22-1.33 (m, 2H), 0.75 (s, 9H); MS: [M+H]  
= 343.

15 **Example 3: (3S)-N-Cyclohexyl-N-{{[2-(trifluoromethyl)phenyl]-methyl}piperidin-3-amine, D-tartrate**

10  $^1\text{H}$ NMR (300MHz, CD<sub>3</sub>OD):  $\delta_{\text{H}}$  7.88-7.91 (d, 1H), 7.51-7.58 (m, 2H), 7.29-7.34 (t, 1H), 4.29 (s, 2H), 3.68-3.83 (q, 2H), 3.43-3.50 (m, 1H), 3.08-3.27 (m, 1H), 2.87-3.00 (m, 2H), 2.39-2.45 (dd, 1H), 2.22-2.29 (dd, 1H), 2.22-2.16 (m, 2H), 1.76-1.90 (m, 2H), 1.58-  
20 1.62 (m, 1H), 1.27-1.41 (m, 2H), 1.08-1.22 (m, 2H), 0.97-1.03 (1H), 0.63-0.74 (m, 4H);  
MS: [M+H] = 341.

**Example 4: (3S)-N-{{[5-Fluoro-2-(trifluoromethyl)phenyl]methyl}-N-tetrahydro-2H-pyran-4-ylpiperidin-3-amine, L-tartrate**

25 a) 1,1-Dimethylethyl (3S)-3-(tetrahydro-2H-pyran-4-ylamino)piperidine-1-carboxylate  
1,1-Dimethylethyl-(3S)-3-aminopiperidine-1-carboxylate (2g, 11mmol), 4H-tetrahydropyran-4-one (1.1g, 11mmol) and dichloroethane (40mL) were stirred under nitrogen at room temperature for 15 min. Sodium triacetoxyborohydride (2.9g, 14mmol) was added in 3 lots over 30 minutes and stirred overnight. The reaction was diluted with

water (50mL) and made basic by addition of 2N NaOH solution. After stirring for 1h, the mixture was extracted into dichloromethane, and the combined organic extracts washed with brine, dried ( $MgSO_4$ ), filtered and evaporated *in vacuo* to give the title compound as an oil.

5

b) *(3S)-N-{[5-Fluoro-2-(trifluoromethyl)phenyl]methyl}-N-tetrahydro-2H-pyran-4-ylpiperidin-3-amine, L-tartrate*

1,1-Dimethylethyl *(3S)-3-(tetrahydro-2H-pyran-4-ylamino)piperidine-1-carboxylate* was reductively alkylated with 5-fluoro-2-(trifluoromethyl)benzaldehyde, then deprotected and crystallised as its L-tartrate salt as described above for Example 1 b) and c), to give the title compound.  $^1H$ NMR (300MHz,  $CD_3OD$ ):  $\delta_H$  7.74-7.75 (m, 2H), 7.05-6.98 (t, 1H), 4.50 (s, 2H), 3.99-3.85 (m, 4H), 3.43-2.58 (m, 8H), 2.02-1.42 (m, 8H); MS:  $[M+H] = 361$ .

15

The following Examples were similarly prepared as described above for Example 4, by reductive alkylation of 1,1-dimethylethyl *(3S)-3-(tetrahydro-2H-pyran-4-ylamino)piperidine-1-carboxylate* with the appropriate benzaldehyde, and subsequent deprotection:

**Example 5: (3S)-N-[(2-Chloro-5-fluorophenyl)methyl]-N-tetrahydro-2H-pyran-4-**

20

**ylpiperidin-3-amine, L-tartrate**

$^1H$ NMR (300MHz,  $CD_3OD$ ):  $\delta_H$  7.32-7.24 (m, 2H), 6.92-6.85 (t, 1H), 4.30 (s, 2H), 3.90-3.84 (m, 4H), 3.32-3.17 (m, 4H), 3.08-2.97 (m, 1H), 2.85-2.67 (m, 3H), 1.98-1.82 (m, 2H), 1.73-1.82 (m, 2H), 1.73-1.46 (m, 6H); MS:  $[M+H] = 327/329$ .

25

**Example 6: (3S)-N-[(1,1'-Biphenyl)-2-ylmethyl]-N-tetrahydro-2H-pyran-4-**

**ylpiperidin-3-amine, sesqui-L-tartrate**

$^1H$ NMR (300MHz,  $CD_3OD$ ):  $\delta_H$  7.51-7.48 (d, 1H), 7.35-7.17 (m, 7H), 7.08-7.05 (d, 1H), 3.30 (s, 1.5H), 3.79-3.74 (dd, 2H), 3.69 (s, 2H), 3.25-3.10 (m, 9H), 3.20-3.09 (m, 2H), 2.91-2.77 (m, 2H), 2.66-2.51 (m, 3H); MS:  $[M+H] = 351$ .

**Example 7: (3S)-N-[(2-Chlorophenyl)methyl]-N-tetrahydro-2H-pyran-4-ylpiperidin-3-amine, D-tartrate**

5       <sup>1</sup>HNMR (300MHz, CD<sub>3</sub>OD): δ<sub>H</sub> 7.52-7.49 (d, 1H), 7.26-7.87 (m, 3H), 4.30 (s, 2H), 3.92-3.80 (m, 4H), 3.16-2.34 (m, 4H), 2.92-2.05 (m, 1H), 2.90-2.66 (m, 3H), 1.93-1.87 (m, 2H), 1.68-1.39 (m, 6H); MS: [M+H] = 309/311.

**Example 8 (3S)-N-Tetrahydro-2H-pyran-4-yl-N-{[2-(trifluoromethyl)phenyl]methyl}piperidin-3-amine, D-tartrate**

10       <sup>1</sup>HNMR (300MHz, CD<sub>3</sub>OD): δ<sub>H</sub> 7.98-7.95 (d, 1H), 7.71-7.62 (q, 2H), 7.47-7.42 (t, 1H), 4.44 (s, 2H), 4.14-3.98 (m, 4H), 3.43-3.29 (m, 4H), 3.11-2.82 (m, 4H), 2.06-2.03 (m, 2H), 1.82-1.66 (m, 6H); MS: [M+H] = 343.

**Example 9 (3S)-N-Cyclopentyl-N-{[2-(trifluoromethyl)phenyl]-methyl}piperidin-3-amine, L-tartrate**

a) 1,1-Dimethylethyl (3S)-3-(cyclopentylamino)-piperidine-1-carboxylate  
1,1-Dimethylethyl (3S)-3-aminopiperidine-1-carboxylate (2.1g, 10.5mmol), cyclopentanone (4.65mL, 52.5mmol), and 10% palladium on carbon (0.2g) in methanol (80mL) were hydrogenated at 60psi overnight in a Parr hydrogenator. The catalyst was filtered off and the filtrate evaporated *in vacuo*. The resultant oil was purified by flash chromatography on silica, eluting with ethyl acetate/cyclohexane (15:85 to 30:70), to give the title compound as an oil.

b) 1,1-Dimethylethyl (3S)-3-(cyclopentyl{[2-(trifluoromethyl)phenyl]methyl}amino)piperidine-1-carboxylate  
1,1-Dimethylethyl (3S)-3-(cyclopentylamino)-piperidine-1-carboxylate (155mg, 0.577mmol), 2-(trifluoromethyl)benzyl bromide (0.105mL, 1.2eq) and anhydrous potassium carbonate (128mg, 1.6eq) in acetonitrile (3mL) were heated at refluxed under nitrogen for 2 days. The reaction mixture was cooled to room temperature, diluted with

ethyl acetate and washed with water, then brine. The organic extracts were dried ( $\text{MgSO}_4$ ), filtered and evaporated *in vacuo*. The resulting oil was purified by flash chromatography on silica eluting with ethyl acetate/cyclohexane (0:100 to 30:70), to give the title compound as an oil.

5

c) (3*S*)-*N*-Cyclopentyl-*N*-{[2-(trifluoromethyl)phenyl]-methyl}piperidin-3-amine, *L*-tartrate

1,1-Dimethylethyl (3*S*)-3-(cyclopentyl{[2-(trifluoromethyl)phenyl]methyl}amino)piperidine-1-carboxylate (160mg, 0.38mmol), trifluoroacetic acid (0.5mL) and dichloromethane (2mL) were stirred at room temperature overnight. The solution was evaporated *in vacuo* to give an oil, which was redissolved in methanol and filtered through a cationic ion exchange resin (Isolute <sup>TM</sup> SCX-2). The basic components were isolated by elution with 2N ammonia in methanol. The eluate was evaporated *in vacuo* and the resultant oil converted to the *L*-tartaric acid salt (freeze drying from acetonitrile/water 1:1), to give the title compound as a white solid. <sup>1</sup>H NMR (300MHz, CD<sub>3</sub>OD):  $\delta_{\text{H}}$  7.89-7.86 (d, 1H), 7.54-7.46 (m, 2H), 7.30-7.25 (t, 1H), 4.34 (s, 2H), 3.90-3.78 (q, 2H), 3.30-3.18 (m, 4H), 3.05-2.87 (m, 1H), 2.81-2.59 (m, 2H), 1.95-1.79 (m, 2H), 1.68-1.30 (m, 9H); MS: [M+H] = 327.

20

The following Examples were similarly prepared as described above for Example 9, by reaction of 1,1-dimethylethyl (3*R*)-3-(cyclopentylamino)piperidine-1-carboxylate with the appropriate benzyl bromide and subsequent deprotection:

**Example 10 (3*S*)-*N*-{[1,1'-Biphenyl]-2-ylmethyl}-*N*-cyclopentyl-piperidin-3-amine,**

25

***L*-tartrate**

<sup>1</sup>H NMR (300MHz, CD<sub>3</sub>OD):  $\delta_{\text{H}}$  7.57-7.55 (d, 1H), 7.35-7.13 (m, 7H), 7.06-7.03 (d, 1H), 4.30 (s, 2H), 3.58 (s, 2H), 3.12-2.98 (m, 3H), 2.82-2.73 (m, 1H), 2.65-2.42 (m, 2H), 1.79-1.75(m, 1H), 1.69-1.65 (m, 1H), 1.53-1.19(m, 10H); MS: [M+H] = 335.

**Example 11 (3S)-N-Cyclopentyl-N-([5-fluoro-1,1'-biphenyl]-2-ylmethyl)-piperidin-3-amine, L-tartrate**

<sup>1</sup>H NMR (300MHz, CD<sub>3</sub>OD): δ<sub>H</sub> 7.35-7.24 (m, 4H), 7.18-7.15 (m, 2H), 7.09-7.04 (m, 1H), 6.92-6.85 (m, 1H), 4.28 (s, 2H), 3.55 (m, 2H), 3.22-3.06 (m, 3H), 2.82-2.77 (m, 1H), 2.68-2.58 (m, 2H), 1.88-1.68 (m, 2H), 1.57-1.19 (m, 10H); MS: [M+H] = 353.

**Example 12 (3S)-N-(Tetrahydrofuran-3-ylmethyl)-N-{[2-(trifluoromethyl)phenyl]methyl}piperidin-3-amine, L-tartrate**

a) 1,1-Dimethylethyl (3S)-3-[(tetrahydrofuran-3-ylmethyl)amino]piperidine-1-carboxylate

10 carboxylate

To 5% palladium on carbon (0.05g) under nitrogen was added a solution of 1,1-dimethylethyl-(3S)-3-aminopiperidine-1-carboxylate (0.50g, 2.5mmol) and tetrahydrofuran-3-carboxaldehyde (50% w/w in water) (0.50g, 2.5mmol) in ethanol (20mL). The reaction mixture was hydrogenated overnight at 60psi in a Parr hydrogenator. The catalyst was removed by filtration through Celite and the solvent removed *in vacuo* to give 1,1-dimethylethyl (3S)-3-[(tetrahydrofuran-3-ylmethyl)amino]piperidine-1-carboxylate as a colourless, slightly cloudy oil.

b) (3S)-N-(Tetrahydrofuran-3-ylmethyl)-N-{[2-(trifluoromethyl)phenyl]methyl}piperidin-3-amine, L-tartrate

To a solution of 1,1-dimethylethyl (3S)-3-[(tetrahydrofuran-3-ylmethyl)amino]piperidine-1-carboxylate (0.67g, 2.36 mmol) in 1,2-dichloroethane (15 mL) was added 2-(trifluoromethyl)benzaldehyde (0.93mL, 7.07mmol). To this mixture was added a solution of sodium triacetoxyborohydride (1.50g, 7.07mmol) in dimethylformamide (3 mL) and left to stir under nitrogen, at room temperature, over the weekend. To the reaction mixture was added water (10 mL) and the solution stirred vigorously for several minutes. The chlorinated organic layer was absorbed directly onto a silica column and the product eluted with methanol/ethyl acetate (0:100 to 30:70). The resultant pale yellow oil was taken up in methanol and absorbed onto a cationic ion exchange resin (Isolute <sup>TM</sup> SCX-2). After washing the cartridge with methanol (25mL),

the basic components were isolated by elution with 2N ammonia in methanol and the eluate evaporated to give 1,1-dimethylethyl (3*S*)-3-{(tetrahydrofuran-3-ylmethyl) {[2-(trifluoromethyl)-phenyl]methyl}amino}piperidine-1-carboxylate as a colourless oil.

To a solution of this oil (0.82g, 1.85mmol) in dichloromethane (10 mL) was added 5 trifluoroacetic acid (2.06mL, 27.8mmol). The reaction mixture was stirred overnight at room temperature, then the solvent removed *in vacuo*. The resulting oil was taken up in methanol and absorbed onto a cationic ion exchange resin (Isolute™ SCX-2). After washing the cartridge with methanol (50mL), the basic components were isolated by elution with 2N ammonia in methanol. The eluate was evaporated *in vacuo* to give a 10 colourless oil. The diastereomers were separated by hplc (Chiralpak AD-H column; 98% heptane, 2% ethanol and 0.2% diethylamine). The faster eluting isomer was taken up in methanol and to this was added a solution of *L*-tartaric acid (0.046g, 0.31 mmol) in methanol. Solvent was removed *in vacuo* and the resulting oil triturated with diethyl ether. Filtration of the resultant suspension gave the title compound as a white solid. 15  $^1\text{H}$ NMR (300MHz, CD<sub>3</sub>OD):  $\delta$ <sub>H</sub> 7.75 (1H, d), 7.58-7.50 (2H, m), 7.34-7.29 (1H, m), 4.30 (3H, s), 3.83 (2H, s), 3.70-3.53 (3H, m), 3.42-3.31 (2H, m), 3.16 (1H, m), 2.90-2.67 (3H, m), 2.54-2.34 (2H, m), 2.34-2.20 (1H, m), 1.95-1.84 (3H, m), 1.63-1.45 (3H, m); MS: [M+H] = 343.

20 The following Examples were prepared from racemic 1,1-dimethylethyl 3-aminopiperidine-1-carboxylate, as described above in Example 1:

**Example 13 N-{{[2-(Methyloxy)phenyl]methyl}-N-{{[2-(trifluoromethyl)phenyl]methyl}piperidin-3-amine**

25  $^1\text{H}$ NMR (300MHz, CDCl<sub>3</sub>)  $\delta$ <sub>H</sub> 8.04-7.95 (d, 1H), 7.57-7.54 (d, 1H), 7.48-7.44 (m, 2H), 7.28-7.11 (m, 2H), 6.93-6.88 (t, 1H), 6.83-6.80 (d, 1H), 3.94-3.86 (d, 2H), 3.20-3.18 (d, 1H), 2.94-2.90 (d, 1H), 2.68-2.55 (m, 2H), 2.49-2.40 (dt, 1H), 2.08-2.04 (d, 1H), 1.76-1.72 (d, 1H), 1.52-1.25 (m, 4H); MS: [M+H] = 379.

**Example 14 N-Cyclohexyl-N-{[2-(trifluoromethyl)phenyl]methyl}-piperidin-3-amine**

<sup>1</sup>HNMR (300MHz, CDCl<sub>3</sub>) δ<sub>H</sub> 8.01-7.93 (d, 1H), 7.59-7.56 (d, 1H), 7.51-7.46 (t, 1H), 7.30-7.19 (m, 1H), 3.91 (s, 2H), 3.15-3.11 (d, 1H), 3.02-2.98 (d, 1H), 2.88-2.80 (d, 1H), 2.55-2.41 (m, 3H), 1.93-1.01 (m, 14); MS: [M+H] = 341.

5

**Example 15 N-(Phenylmethyl)-N-{[2-(trifluoromethyl)phenyl]-methyl}piperidin-3-amine**

<sup>1</sup>HNMR (300MHz, CDCl<sub>3</sub>) δ<sub>H</sub> 7.93-7.96 (d, 1H), 7.55-7.61 (d, 1H), 7.47-7.51 (t, 1H), 7.18-7.35 (m, 6H), 3.77-3.90 (q, 2H), 3.64-3.74 (q, 2H), 3.17-3.20 (d, 1H), 2.91-2.95 (d, 1H), 2.53-2.67 (m, 2H), 2.39-2.48 (dt, 1H), 1.97-2.06 (d, 1H), 1.22-1.82 (m, 3H); MS: [M+H] = 349.

**Example 16 (3S)-N-(2-Methylpropyl)-N-{[2-(trifluoromethyl)phenyl]-methyl}-1-azabicyclo[2.2.2]octan-3-amine, sesquifumarate**

- 15 a) (3S)-N-{[2-(Trifluoromethyl)phenyl]methyl}-1-azabicyclo[2.2.2]octan-3-amine  
Sodium triacetoxyborohydride (18.7g, 88.3mmol) was added portionwise over 20 min. to a stirred solution of (3S)-1-azabicyclo[2.2.2]octan-3-amine dihydrochloride (5g, 25.1mmol) and 2-trifluoromethylbenzaldehyde (4.81g, 27.6mmol) in DMF (100mL). After stirring under nitrogen for 4 days, the mixture was diluted with excess water, 20 basified with 2N sodium hydroxide and stirred for 1h. The product was extracted into dichloromethane and evaporated *in vacuo* to give an oil, which was dissolved in 2N hydrochloric acid. After washing with ether, the aqueous phase was basified with 2N sodium hydroxide and extracted with dichloromethane. The organic phase was dried (MgSO<sub>4</sub>) and evaporated *in vacuo* to give an oil. <sup>1</sup>HNMR (300 MHz, CD<sub>3</sub>OD) δ<sub>H</sub>: 7.62-7.69 (t, 2H), 7.50-7.55 (t, 1H), 7.32-7.37 (t, 1H), 3.83-3.96 (q, 2H), 3.1-3.19 (m, 1H), 2.72-2.93 (m, 5H), 2.42-2.49 (m, 1H), 1.85-1.95 (m, 1H), 1.63-1.73 (m, 1H), 1.32-1.53; 25 MS: [M+H]= 285.  
b) (3S)-N-(2-Methylpropyl)-N-{[2-(trifluoromethyl)-phenyl]methyl}-1-azabicyclo[2.2.2]octan-3-amine, sesquifumarate

-70-

(3*S*)-*N*-{[2-(Trifluoromethyl)phenyl]methyl}-1-azabicyclo[2.2.2]octan-3-amine (0.30g, 1.06mmol), isobutyraldehyde (0.152g, 2.1mmol) and 1,2-dichloroethane (6mL) were stirred under nitrogen at room temperature for 15 min. Sodium triacetoxyborohydride (0.492g, 2.32mmol) was added in two lots over 5 min. TLC after 1 day showed the reaction to be incomplete, so additional sodium triacetoxyborohydride (0.24g, 1.15mmol) was added and the mixture heated at 50°C for 5 days. After cooling to room temperature, methanol was added and the mixture was stirred for 1h. This solution was filtered through a cationic ion exchange resin (Isolute™ SCX-2) and the basic fractions isolated by elution with 2N ammonia in methanol to give, after evaporation *in vacuo*, an oil. The crude product was purified using preparative LCMS to give the product as an acetate salt, which was converted to the free base using cationic ion exchange resin as described above. The free base was converted to the fumarate salt, to give the title compound as a white solid from ethanol/diethyl ether. <sup>1</sup>HNMR (300 MHz, CD<sub>3</sub>OD) δ<sub>H</sub>: 7.88-7.91 (d, 1H), 7.51-7.58 (m, H), 7.30-7.35 (t, 1H), 6.60 (s, 3H), 3.71-3.85 (q, 2H), 3.42-4.50 (m, 1H), 2.88-3.26 (m, 6H), 2.25-2.39 (m, 1H), 2.09-2.23 (m, 3H), 1.74-1.91 (m, 2H), 1.42-1.63 (m, 2H), 0.78-0.83 (t, 6H); MS: [M+H] = 341.

The following Examples were similarly prepared as described above for Example 16, from (3*S*)-*N*-{[2-(trifluoromethyl)phenyl]methyl}-1-azabicyclo-[2.2.2]octan-3-amine and the appropriate substituted benzaldehyde:

**Example 17 (3*S*)-*N*-{[1,1'-Biphenyl]-2-ylmethyl}-*N*-(2-methylpropyl)-1-azabicyclo[2.2.2]octan-3-amine, *D*-tartrate**

<sup>1</sup>HNMR (300 MHz, CD<sub>3</sub>OD) δ<sub>H</sub>: 7.50-7.47 (d, 1H), 7.38-7.18 (m, 7H), 7.09-7.06 (dd, 1H), 4.29 (s, 2H), 3.58-3.54 (d, 1H), 3.43-3.39 (d, 1H), 3.25-3.18 (m, 1H), 3.09-3.90 (4H), 2.68-2.63 (t, 1H), 2.45-2.39 (dq, 1H), 2.16-1.98 (m, 3H), 1.83-1.74 (m, 2H), 1.65-1.61 (m, 1H), 1.45-1.42 (m, 1H), 1.31-1.22 (quin, 1H), 0.65-0.61 (t, 6H); MS: [M+H] = 349.

**Example 18 (3S)-N-[(3,5-Dichlorophenyl)methyl]-N-(2-methylpropyl)-1-azabicyclo[2.2.2]octan-3-amine, sesqui D-tartrate**

<sup>1</sup>HNMR (300 MHz, CD<sub>3</sub>OD) δ<sub>H</sub>: 7.36-7.34 (m, 3H), 4.44 (s, 3H), 3.71 (s, 2H), 3.65-3.54 (m, 1H), 3.42-3.01 (m, 6H), 2.42-1.84 (m, 6H), 1.74-1.63 (m, 2H), 0.95-0.87 (dd, 5 H); MS: [M+H] = 341/343/345.

**Example 19 (3S)-N-[(2,4-Dichlorophenyl)methyl]-N-(2-methylpropyl)-1-azabicyclo[2.2.2]octan-3-amine**

<sup>1</sup>HNMR (300 MHz, CDCl<sub>3</sub>) δ<sub>H</sub>: 7.65-7.62 (d, 1H), 7.32-7.31 (d, 1H), 7.24-7.20 (dd, 1H), 3.72-3.56 (q, 2H), 3.08-3.01 (m, 1H), 2.87-2.55 (m, 6H), 2.35-2.20 (oct, 2H), 1.87-1.77 (m, 2H), 1.67-1.39 (3H), 1.25-1.17 (m, 1H), 0.87-0.82 (dd, 6H); MS: [M+H] = 341/343/345.

**Example 20 (3S)-N-{[4-Fluoro-2-(trifluoromethyl)phenyl]methyl}-N-(2-methylpropyl)-1-azabicyclo[2.2.2]octan-3-amine, L-tartrate**

<sup>1</sup>HNMR (300 MHz, CD<sub>3</sub>OD) δ<sub>H</sub>: 7.94-7.89 (t, 1H), 7.34-7.27 (m, 2H), 4.29 (s, 4.29), 3.81-3.66 (q, 2H), 3.51-3.44 (t, 1H), 3.40-2.89 (m, 6H), 2.37-2.04 (m, 4H), 1.93-1.38 (m, 4H), 0.82-0.76 (dd, 6H); MS: [M+H] = 359.

**Example 21 (3S)-N-[(4-Fluoro[1,1'-biphenyl]-2-yl)methyl]-N-(2-methylpropyl)-1-azabicyclo[2.2.2]octan-3-amine, L-tartrate**

<sup>1</sup>HNMR (300 MHz, CD<sub>3</sub>OD) δ<sub>H</sub>: 7.40-7.08 (m, 7H), 6.68-6.91 (dt, 1H), 4.29 (s, 2H), 3.56-4.0 (q, 2H), 3.31-2.96 (m, 5H), 2.72-2.67 (t, 1H), 2.58-2.52 (dq, 1H), 2.18-1.30 (m, 8H), 0.70-0.68 (dd, 6H); MS: [M+H] = 367.

The compounds of the present invention are inhibitors of the uptake of one or more monoamines selected from serotonin, norepinephrine and dopamine. They work by selectively inhibiting one or more of the biogenic amine (serotonin, norepinephrine and dopamine) transporter proteins. Their selectivity profiles may be determined using the assays described below (see also J. Gobel, D.L. Saussy and A. Goetz, J. Pharmacol. Toxicol. (1999), 42, 237-244). Compounds of Formula I and their pharmaceutically

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- acceptable salts preferably exhibit a  $K_i$  value less than 600nM at one or more of these monoamine transporter proteins as determined using the scintillation proximity assay as described below. The compounds of formula (I) exemplified above and their pharmaceutically acceptable salts exhibit a  $K_i$  value less than 500nM at one or more of these monoamine transporter proteins as determined using the scintillation proximity assay as described below. Especially preferred compounds of Formula I and their pharmaceutically acceptable salts exhibit a  $K_i$  value less than 100nM at one or more of these monoamine transporter proteins. Even more preferred compounds of Formula I and their pharmaceutically acceptable salts exhibit a  $K_i$  value less than 50nM at one or more of these monoamine transporter proteins. Preferably, compounds of the present invention which selectively inhibit one of the three biogenic amine transporters do so relative to the other two transporters by a factor of at least five, more preferably by a factor of at least ten. For example, a NET selective inhibitor has a ratio  $K_i(\text{SERT})/K_i(\text{NET})$  and a ratio  $K_i(\text{DAT})/K_i(\text{NET})$  greater than or equal to five, preferably greater than or equal to ten.
- Preferably, compounds of the present invention which selectively inhibit two of the three biogenic amine transporters do so relative to the other transporter by a factor of at least five, more preferably by a factor of at least ten. For example, a NET/SERT selective inhibitor has a ratio  $K_i(\text{DAT})/K_i(\text{NET})$  and a ratio  $K_i(\text{DAT})/K_i(\text{SERT})$  greater than or equal to five, preferably greater than or equal to ten
- Biogenic amine transporters control the amount of neurotransmitters in the synaptic cleft. Inhibition of the respective transporter leads to a rise in that neurotransmitter. Inhibition of the individual transporters can be studied by a simple competitive binding assay using selective radioligands for the individual expressed human transporter site. Compounds may be compared for selectivity and potency on the human norepinephrine transporter (hNET), the h-serotonin transporter (hSERT) and the h-dopamine transporter (hDAT) using membranes prepared from HEK293 cells expressing the respective transporter site.
- Advantageously, the compounds of the present invention also have a reduced interaction (both as substrate and inhibitor) with the liver enzyme Cytochrome P450 (CYP2D6).

That is to say, they preferably exhibit less than 75% metabolism via the CYP2D6 pathway according to the CYP2D6 substrate assay described below and they preferably exhibit an IC<sub>50</sub> of >6μM according to the CYP2D6 inhibitor assay described below.

5    Generation of stable cell-lines expressing the human dopamine, norepinephrine and serotonin transporters

Standard molecular cloning techniques were used to generate stable cell-lines expressing the human dopamine, norepinephrine and serotonin transporters. The polymerase chain 10 reaction (PCR) was used in order to isolate and amplify each of the three full-length cDNAs from an appropriate cDNA library. Primers for PCR were designed using the following published sequence data:

Human dopamine transporter: GenBank M95167. Reference: Vandenberghe DJ, Persico 15 AM and Uhl GR. *A human dopamine transporter cDNA predicts reduced glycosylation, displays a novel repetitive element and provides racially-dimorphic TaqI RFLPs.* Molecular Brain Research (1992) volume 15, pages 161-166.

Human norepinephrine transporter: GenBank M65105. Reference: Pacholczyk T, Blakely, RD and Amara SG. *Expression cloning of a cocaine- and antidepressant-sensitive human noradrenaline transporter.* Nature (1991) volume 350, pages 350-354.

Human serotonin transporter: GenBank L05568. Reference: Ramamoorthy S, Bauman AL, Moore KR, Han H, Yang-Feng T, Chang AS, Ganapathy V and Blakely RD. 25 *Antidepressant- and cocaine-sensitive human serotonin transporter: Molecular cloning, expression, and chromosomal localization.* Proceedings of the National Academy of Sciences of the USA (1993) volume 90, pages 2542-2546.

The PCR products were cloned into a mammalian expression vector (eg pcDNA3.1 30 (Invitrogen)) using standard ligation techniques. The constructs were then used to stably

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transfect HEK293 cells using a commercially available lipofection reagent (Lipofectamine<sup>TM</sup> – Invitrogen) following the manufacturer's protocol.

#### Norepinephrine Binding Assay

- 5 The ability of compounds to compete with [<sup>3</sup>H]-Nisoxetine for its binding sites on cloned human norepinephrine membranes has been used as a measure of its ability to block norepinephrine uptake via its specific transporter.

#### Membrane Preparation

- 10 Cell pastes from large scale production of HEK-293 cells expressing cloned human noradrenaline transporters were homogenised in 4 volumes 50mM Tris.HCl containing 300mM NaCl and 5mM KCl, pH 7.4. The homogenate was centrifuged twice (40,000g, 10min, 4°C) with pellet re-suspension in 4 volumes Tris.HCl buffer after the first spin and 8 volumes after the second spin. The suspended homogenate was centrifuged (100g, 15min, 4°C) and the supernatant kept and re-centrifuged (40,000g, 20min, 4°C). The pellet was resuspended in Tris.HCl buffer containing the above reagents along with 10%w/v sucrose and 0.1mM phenylmethylsulfonyl fluoride (PMSF). The membrane preparation was stored in aliquots (1ml) at -80°C until required. The protein concentration of the membrane preparation was determined using a bicinchoninic acid (BCA) protein assay reagent kit (available from Pierce).

#### [<sup>3</sup>H]-Nisoxetine Binding Assay

Each well of a 96well microtitre plate was set up to contain the following:

- 25 50µl 2nM [N-methyl-<sup>3</sup>H]-Nisoxetine hydrochloride (70-87Ci/mmol, from NEN Life Science Products)
- 75µl Assay buffer (50mM Tris.HCl pH 7.4 containing 300mM NaCl and 5mM KCl)
- 25µl Test compound, assay buffer (total binding) or 10µM Desipramine HCl (non-specific binding)
- 30 50µl Wheatgerm agglutinin coated poly(vinyltoluene) (WGA PVT) SPA Beads (Amersham Biosciences RPNQ0001) (10mg/ml)

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50µl Membrane (0.2mg protein per ml.)

The microtitre plates were incubated at room temperature for 10 hours prior to reading in a Trilux scintillation counter. The results were analysed using an automatic spline fitting  
5 programme (Multicalc, Packard, Milton Keynes, UK) to provide Ki values for each of the test compounds.

#### Serotonin Binding Assay

The ability of a test compound to compete with [<sup>3</sup>H]-citalopram from its binding sites on  
10 cloned human serotonin membranes has been used as a measure of its ability to block serotonin uptake via its specific transporter (Ramamoorthy, S., Giovanetti, E., Qian, Y., Blakely, R., (1998) J. Biol. Chem. 273,2458).

#### Membrane Preparation

15 The preparation of membrane is essentially similar to that for the norepinephrine transporter containing membrane described above. The membrane preparation was stored in aliquots (1ml) at -70°C until required. The protein concentration of the membrane preparation was determined using BCA protein assay reagent kit.

#### [<sup>3</sup>H]-Citalopram Binding Assay

Each well of a 96well microtitre plate was set up to contain the following:

50µl 2nM [<sup>3</sup>H]-Citalopram (60-86Ci/mmol, Amersham Biosciences)  
75µl Assay buffer (50mM Tris.HCl pH 7.4 containing 150mM NaCl and 5mM  
25 KCl)  
25µl Diluted compound, assay buffer (total binding) or 100µM Fluoxetine (non-specific binding)  
50µl WGA PVT SPA Beads (40mg/ml)  
50µl Membrane preparation (0.4mg protein per ml)

The microtitre plates were incubated at room temperature for 10 hours prior to reading in a Trilux scintillation counter. The results were analysed using an automatic spline fitting programme (Multicalc, Packard, Milton Keynes, UK) to provide Ki (nM) values for each of the test compounds.

5

#### Dopamine Binding Assay

The ability to compete with [<sup>3</sup>H]-WIN35,428 for its binding sites on human cell membranes containing cloned human dopamine transporter has been used as a measure of its ability to block dopamine uptake via its specific transporter (Ramamoorthy et al 1998 *supra*).

#### Membrane Preparation.

Is essentially the same as for membranes containing cloned human serotonin transporter as described above.

15

#### [<sup>3</sup>H]-WIN35,428 Binding Assay

Each well of a 96well microtitre plate was set up to contain the following:

50µl	4nM [ <sup>3</sup> H]-WIN35,428 (84-87Ci/mmol, from NEN Life Science Products)
75µl	Assay buffer (50mM Tris.HCl pH 7.4 containing 150mM NaCl and 5mM KCl)
25µl	Diluted compound, assay buffer(total binding) or 100µM Nomifensine (non-specific binding)
25	50µl WGA PVT SPA Beads (10mg/ml)
	50µl Membrane preparation (0.2mg protein per ml.)

The microtitre plates were incubated at room temperature for 120 minutes prior to reading in a Trilux scintillation counter. The results were analysed using an automatic spline fitting programme (Multicalc, Packard, Milton Keynes, UK) to provide Ki values for each of the test compounds.

**CYP2D6 Assays**

Cytochrome P450 2D6 (CYP2D6) is a mammalian enzyme which is commonly associated with the metabolism of around 30% pharmaceutical compounds. Moreover, 5 this enzyme exhibits genetic polymorphism, resulting in the presence of both normal and poor metabolizers in the population. A low involvement of CYP2D6 in the metabolism of compounds (i.e. the compound being a poor substrate of CYP2D6) is desirable in order to reduce any variability from subject to subject in the pharmacokinetics of the compound. Also, compounds with a low inhibitor potential for CYP2D6 are desirable in order to 10 avoid drug-drug interactions with co-administered drugs that are substrates of CYP2D6. Compounds may be tested both as substrates and as inhibitors of this enzyme by means of the following assays.

**CYP2D6 substrate assay****15 Principle:**

This assay determines the extent of the CYP2D6 enzyme involvement in the total oxidative metabolism of a compound in microsomes. Preferred compounds of the present invention exhibit less than 75% total metabolism via the CYP2D6 pathway.

20 For this *in vitro* assay, the extent of oxidative metabolism in human liver microsomes (HLM) is determined after a 30 minute incubation in the absence and presence of Quinidine, a specific chemical inhibitor of CYP2D6. The difference in the extent of metabolism in absence and presence of the inhibitor indicates the involvement of CYP2D6 in the metabolism of the compound.

25

**Materials and Methods:**

Human liver microsomes (mixture of 20 different donors, mixed gender) were acquired from Human Biologics (Scottsdale, AZ, USA). Quinidine and  $\beta$ -NADPH ( $\beta$ -Nicotinamide Adenine Dinucleotide Phosphate, reduced form, tetrasodium salt) were 30 purchased from Sigma (St Louis, MO, USA). All the other reagents and solvents were of analytical grade. A stock solution of the test compound (TC) was prepared in a mixture of

Acetonitrile/Water to reach a final concentration of acetonitrile in the incubation below 0.5%.

The microsomal incubation mixture (total volume 0.1 mL) contained the TC (4  $\mu$ M),  
5  $\beta$ -NADPH (1 mM), microsomal proteins (0.5 mg/mL), and Quinidine (0 or 2  $\mu$ M) in 100 mM sodium phosphate buffer pH 7.4. The mixture was incubated for 30 minutes at 37 °C in a shaking waterbath. The reaction was terminated by the addition of acetonitrile (75  $\mu$ L). The samples were vortexed and the denatured proteins were removed by centrifugation. The amount of TC in the supernatant was analyzed by liquid  
10 chromatography /mass spectrometry (LC/MS) after addition of an internal standard. A sample was also taken at the start of the incubation ( $t=0$ ), and analysed similarly.

Analysis of the TC was performed by liquid chromatography /mass spectrometry. Ten  $\mu$ L of diluted samples (20 fold dilution in the mobile phase) were injected onto a Spherisorb  
15 CN Column, 5  $\mu$ M and 2.1 mm x 100 mm (Waters corp. Milford, MA, USA). The mobile phase consisting of a mixture of Solvent A/Solvent B, 30/70 (v/v) was pumped (Alliance 2795, Waters corp. Milford, MA, USA) through the column at a flow rate of 0.2 ml/minute. Solvent A and Solvent B were a mixture of ammonium formate 5. $10^{-3}$  M pH 4.5/ methanol in the proportions 95/5 (v/v) and 10/90 (v/v), for solvent A and solvent B,  
20 respectively. The TC and the internal standard were quantified by monitoring their molecular ion using a mass spectrometer ZMD or ZQ (Waters-Micromass corp, Manchester, UK) operated in a positive electrospray ionisation.

The extent of CYP2D6 involvement (% of CYP2D6 involvement) was calculated  
25 comparing the extent of metabolism in absence and in presence of quinidine in the incubation.

The extent of metabolism without inhibitor (%) was calculated as follows:

$$30 \quad \frac{(\text{TC response in samples without inhibitor})_{\text{time } 0} - (\text{TC response in samples without inhibitor})_{\text{time } 30}}{(\text{TC response in samples without inhibitor})_{\text{time } 0}} \times 100$$

The extent of metabolism with inhibitor (%) was calculated as follows:

$$\frac{(\text{TC response in samples without inhibitor})_{\text{time } 0} - (\text{TC response in samples with inhibitor})_{\text{time } 30}}{(\text{TC response in samples without inhibitor})_{\text{time } 0}} \times 100$$

5

where the TC response is the area of the TC divided by the area of the internal standard in the LC/MS analysis chromatogram, time0 and time30 correspond to the 0 and 30 minutes incubation time.

10 The % of CYP2D6 involvement was calculated as follows :

$$\frac{(\% \text{ extent of metabolism without inhibitor}) - (\% \text{ extent of metabolism with inhibitor})}{\% \text{ extent of metabolism without inhibitor}} \times 100$$

#### CYP2D6 inhibitor assay

15 **Principle:**

The CYP2D6 inhibitor assay evaluates the potential for a compound to inhibit CYP2D6.

This is performed by the measurement of the inhibition of the bufuralol 1'-hydroxylase activity by the compound compared to a control. The 1'-hydroxylation of bufuralol is a metabolic reaction specific to CYP2D6. Preferred compounds of the present invention

20 exhibit an IC<sub>50</sub> higher than 6 µM for CYP2D6 activity, the IC<sub>50</sub> being the concentration of the compound that gives 50 % of inhibition of the CYP2D6 activity.

#### **Material and methods:**

Human liver microsomes (mixture of 20 different donors, mixed gender) were acquired  
25 from Human Biologics (Scottsdale, AZ). β-NADPH was purchased from Sigma (St Louis, MO). Bufuralol was purchased from Ultrafine (Manchester, UK). All the other reagents and solvents were of analytical grade.

Microsomal incubation mixture (total volume 0.1 mL) contained bufuralol 10 µM,  
30 β-NADPH (2 mM), microsomal proteins (0.5 mg/mL), and the test compound (TC) (0, 5,

- and 25  $\mu$ M) in 100 mM sodium phosphate buffer pH 7.4. The mixture was incubated in a shaking waterbath at 37 °C for 5 minutes. The reaction was terminated by the addition of methanol (75  $\mu$ L). The samples were vortexed and the denatured proteins were removed by centrifugation. The supernatant was analyzed by liquid chromatography connected to a fluorescence detector. The formation of the 1'-hydroxybufuralol was monitored in control samples (0  $\mu$ M TC) and in the samples incubated in presence of the TC. The stock solution of TC was prepared in a mixture of Acetonitrile/Water to reach a final concentration of acetonitrile in the incubation below 1.0%.
- 5      The determination of 1'hydroxybufuralol in the samples was performed by liquid chromatography with fluorimetric detection as described below. Twenty five  $\mu$ L samples were injected onto a Chromolith Performance RP-18e column (100 mm x 4.6 mm) (Merck KGaA, Darmstadt, Germany). The mobile phase, consisting of a mixture of solvent A and solvent B whose the proportions changed according the following linear gradient, was pumped through the column at a flow rate of 1 ml/min:
- 10     15

Time (minutes)	Solvent A (%)	Solvent B (%)
0	65	35
2.0	65	35
2.5	0	100
5.5	0	100
6.0	65	35

- Solvent A and Solvent B consisted of a mixture of 0.02 M potassium dihydrogenophosphate buffer pH3/ methanol in the proportion 90/10 (v/v) for solvent A and 10/90 (v/v) for solvent B. The run time was 7.5 minutes. Formation of 1'-hydroxybufuralol was monitored by fluorimetric detection with extinction at  $\lambda$  252 nm and emission at  $\lambda$  302 nm.
- 20

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The IC<sub>50</sub> of the TC for CYP2D6 was calculated by the measurement of the percent of inhibition of the formation of the 1'-hydroxybufuralol in presence of the TC compared to control samples (no TC) at a known concentration of the TC.

The percent of inhibition of the formation of the 1'-hydroxybufuralol is calculated as

5 follows:

$$\frac{(1\text{-hydroxybufuralol formed without inhibitor}) - (1\text{-hydroxybufuralol formed with inhibitor})}{(1\text{-hydroxybufuralol area formed without inhibitor})} \times 100$$

The IC<sub>50</sub> is calculated from the percent inhibition of the formation of the 1'-hydroxybufuralol as follows (assuming competitive inhibition):

10 
$$\frac{\text{TC Concentration} \times (100 - \text{Percent of inhibition})}{\text{Percent of inhibition}}$$

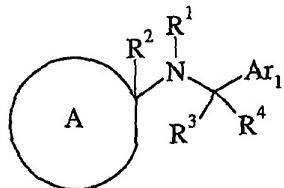
The IC<sub>50</sub> estimation is assumed valid if inhibition is between 20% and 80% (Moody GC, Griffin SJ, Mather AN, McGinnity DF, Riley RJ. 1999. Fully automated analysis of activities catalyzed by the major human liver cytochrome P450 (CYP) enzymes:

15 assessment of human CYP inhibition potential. Xenobiotica, 29(1): 53-75).

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## CLAIMS:

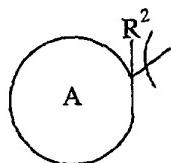
1. A compound of formula (I):



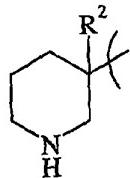
5

(I)

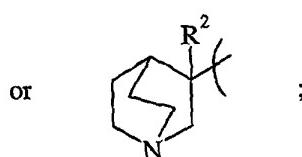
wherein



is a group of formula (a) or (b)



(a)

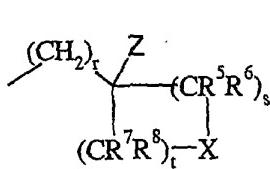


(b)

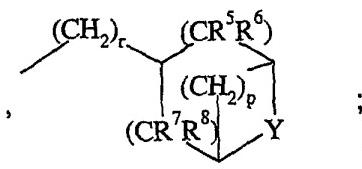
10

$R^1$  is  $C_1-C_6$  alkyl (optionally substituted with 1, 2 or 3 halo substituents and/or with 1 substituent selected from  $-S-(C_1-C_3$  alkyl),  $-O-(C_1-C_3$  alkyl) (optionally substituted with 1, 2 or 3 F atoms),  $-O-(C_3-C_6$  cycloalkyl),  $-SO_2-(C_1-C_3$  alkyl),  $-CN$ ,  $-COO-(C_1-C_2$  alkyl) and  $-OH$ );  $C_2-C_6$  alkenyl;  $-(CH_2)_q-Ar_2$ ; or a group of formula (i) or (ii)

15



(i)



(ii)

$R^2$ ,  $R^3$  and  $R^4$  are each independently selected from hydrogen or  $C_1-C_2$  alkyl;

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- R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are at each occurrence independently selected from hydrogen or C<sub>1</sub>-C<sub>2</sub> alkyl;
- X- is a bond, -CH<sub>2</sub>-, -CH=CH-, -O-, -S-, or -SO<sub>2</sub>-;
- Y- is a bond, -CH<sub>2</sub>- or -O-;
- 5      -Z is hydrogen, -OH or -O-(C<sub>1</sub>-C<sub>3</sub> alkyl);
- p is 0, 1 or 2;
- q is 0, 1 or 2;
- r is 0 or 1;
- s is 0, 1, 2 or 3;
- 10     t is 0, 1, 2, 3 or 4;
- Ar<sub>1</sub> is selected from:
- (i)    a phenyl group or a 5- or 6-membered monocyclic heteroaromatic group each of which is optionally substituted with 1, 2, 3, 4 or 5 substituents (depending on the number of available substitution positions) each independently selected from halo, cyano, C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C<sub>1</sub>-C<sub>4</sub> alkyl) (optionally substituted with 1, 2 or 3 F atoms) and -S-(C<sub>1</sub>-C<sub>4</sub> alkyl) (optionally substituted with 1, 2 or 3 F atoms) and/or with 1 substituent selected from pyridinyl, pyrazolyl, phenyl (optionally substituted with 1, 2 or 3 halo substituents), benzyl (optionally substituted with 1, 2 or 3 halo substituents) and phenoxy (optionally substituted with 1, 2 or 3 halo substituents) with the proviso that only C<sub>1</sub>-C<sub>4</sub>alkyl may be a substituent for the H of any -NH-moiety present within a 5- or 6-membered monocyclic heteroaromatic group; or
- 15     (ii)   a naphthyl group or an 8-, 9- or 10-membered bicyclic heteroaromatic group each of which is optionally substituted with 1, 2, 3, 4, 5 or 6 substituents (depending on the number of available substitution positions) each independently selected from halo, cyano, C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C<sub>1</sub>-C<sub>4</sub> alkyl) (optionally substituted with 1, 2 or 3 F atoms) and -S-(C<sub>1</sub>-C<sub>4</sub> alkyl) (optionally substituted with 1,
- 20
- 25
- 30

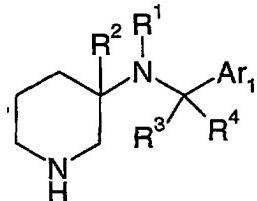
2 or 3 F atoms) with the proviso that only C<sub>1</sub>-C<sub>4</sub>alkyl may be a substituent for the H of any -NH- moiety present within an 8-, 9- or 10-membered bicyclic heteroaromatic group; and

Ar<sub>2</sub> is selected from

- 5 (i) a phenyl group or a 5- or 6-membered monocyclic heteroaromatic group each of which is optionally substituted with 1, 2, 3, 4 or 5 substituents (depending on the number of available substitution positions) each independently selected from halo, cyano, C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C<sub>1</sub>-C<sub>4</sub> alkyl) (optionally substituted with 1, 10 2 or 3 F atoms) and -S-(C<sub>1</sub>-C<sub>4</sub> alkyl) (optionally substituted with 1, 2 or 3 F atoms) with the proviso that only C<sub>1</sub>-C<sub>4</sub>alkyl may be a substituent for the H of any -NH- moiety present within a 5- or 6-membered monocyclic heteroaromatic group; or
- 15 (ii) a naphthyl group or an 8-, 9- or 10-membered bicyclic heteroaromatic group each of which is optionally substituted with 1, 2, 3, 4, 5 or 6 substituents (depending on the number of available substitution positions) each independently selected from halo, cyano, C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C<sub>1</sub>-C<sub>4</sub> alkyl) (optionally substituted with 1, 20 2 or 3 F atoms) and -S-(C<sub>1</sub>-C<sub>4</sub> alkyl) (optionally substituted with 1, 2 or 3 F atoms) with the proviso that only C<sub>1</sub>-C<sub>4</sub>alkyl may be a substituent for the H of any -NH- moiety present within an 8-, 9- or 10-membered bicyclic heteroaromatic group;
- 25 or a pharmaceutically acceptable salt thereof; provided that
- (a) the cyclic portion of the group of formula (i) must contain at least three carbon atoms and not more than seven ring atoms;
- (b) when -X- is -CH=CH-, then the cyclic portion of the group of formula (i) must contain at least five carbon atoms; and
- (c) when -Z is -OH or -O-(C<sub>1</sub>-C<sub>3</sub> alkyl), then -X- is -CH<sub>2</sub>-; and
- (d) when -Y- is -O- then p cannot be 0.

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2. A compound according to claim 1 of formula (I')

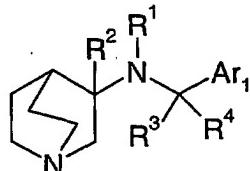


(I')

wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and Ar<sub>1</sub> have the values defined in formula (I) in claim 1.

5

3. A compound according to claim 1 of formula (I'')



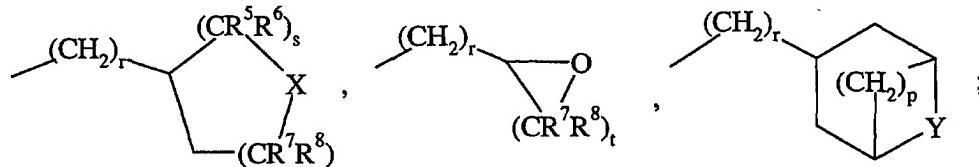
(I'')

wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and Ar<sub>1</sub> have the values defined in formula (I) in claim 1.

10

4. A compound according to any one of claims 1 to 3 wherein R<sup>1</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, -(CH<sub>2</sub>)<sub>m</sub>-CF<sub>3</sub>, -(CH<sub>2</sub>)<sub>n</sub>-S-(C<sub>1</sub>-C<sub>3</sub> alkyl), -CH<sub>2</sub>-COO-(C<sub>1</sub>-C<sub>2</sub> alkyl), -(C<sub>1</sub>-C<sub>5</sub> alkylene)-O-(C<sub>1</sub>-C<sub>3</sub> alkyl), -(C<sub>1</sub>-C<sub>5</sub> alkylene)-O-(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), -(C<sub>1</sub>-C<sub>5</sub> alkylene)-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>3</sub> alkyl), -(C<sub>1</sub>-C<sub>5</sub> alkylene)-OCF<sub>3</sub>, -(C<sub>1</sub>-C<sub>6</sub> alkylene)-OH, -(C<sub>1</sub>-C<sub>5</sub> alkylene)-CN, -(CH<sub>2</sub>)<sub>q</sub>-Ar<sub>2</sub> or a group of formula (ia), (ib) or (ii)

15



(ia)

(ib)

(ii)

R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, -X-, -Y-, p, q, r and s are as defined in claim 1;

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m is 1, 2 or 3;

n is 1, 2 or 3;

t is 2, 3 or 4;

-Ar<sub>1</sub> is phenyl, pyridyl, thiazolyl or naphthyl; wherein said phenyl, pyridyl or thiazolyl group may be substituted with 1, 2 or 3 substituents each independently selected from halo, trifluoromethyl, cyano, C<sub>1</sub>-C<sub>4</sub> alkyl, -O-(C<sub>1</sub>-C<sub>4</sub> alkyl), -O-(C<sub>1</sub>-C<sub>4</sub> difluoroalkyl), -O-(C<sub>1</sub>-C<sub>4</sub> trifluoroalkyl), -S-(C<sub>1</sub>-C<sub>4</sub> alkyl), -S-(C<sub>1</sub>-C<sub>2</sub> trifluoroalkyl) and/or with 1 substituent selected from pyridyl, pyrazole, phenyl (optionally substituted with 1, 2 or 3 halo substituents) and phenoxy (optionally substituted with 1, 2 or 3 halo substituents); and wherein said naphthyl group may be optionally substituted with 1, 2 or 3 substituents each independently selected from halo, trifluoromethyl, cyano, C<sub>1</sub>-C<sub>4</sub> alkyl, -O-(C<sub>1</sub>-C<sub>4</sub> alkyl), -O-(C<sub>1</sub>-C<sub>4</sub> difluoroalkyl), -O-(C<sub>1</sub>-C<sub>4</sub> trifluoroalkyl), -S-(C<sub>1</sub>-C<sub>4</sub> alkyl), -S-(C<sub>1</sub>-C<sub>2</sub> trifluoroalkyl);

5 Ar<sub>2</sub> is naphthyl, pyridyl, thiazolyl, furyl, thiophenyl, benzothiophenyl, or phenyl, wherein said naphthyl, pyridyl, thiazolyl, furyl, thiophenyl, benzothiophenyl, or phenyl may be substituted with 1, 2 or 3 substituents each independently selected from halo, C<sub>1</sub>-C<sub>4</sub> alkyl, trifluoromethyl and -O-(C<sub>1</sub>-C<sub>4</sub> alkyl).

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5. A compound according to any one of claims 1 to 4 wherein R<sup>2</sup> is hydrogen.
6. A compound according to any one of claims 1 to 5 wherein R<sup>3</sup> and R<sup>4</sup> are hydrogen.
- 20
7. A compound according to any one of claims 1 to 6 wherein each R<sup>5</sup> and R<sup>6</sup> is hydrogen.
- 25
8. A compound according to any one of claims 1 to 7 wherein each R<sup>7</sup> and R<sup>8</sup> is hydrogen.
9. A compound according to any one of claims 1 to 8 wherein R<sup>1</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl.

10. A compound according to any one of claims 1 to 8 wherein R<sup>1</sup> is -(C<sub>4</sub>-C<sub>5</sub> alkylene)-OH.
- 5        11. A compound according to any one of claims 1 to 8 wherein R<sup>1</sup> is a group of formula (i), r is 0 or 1, s is 2, t is 1 or 2, -Z is hydrogen and -X- is -O-, -S- or -SO<sub>2</sub>-.
- 10        12. A compound according to any one of claims 1 to 8 wherein R<sup>1</sup> is a group of formula (i), r is 0, s is 1, 2 or 3, t is 1, -Z is hydrogen and -X- is -CH<sub>2</sub>-.
13. A compound according to any one of claims 1 to 8 wherein R<sup>1</sup> is a group of formula (i), r is 1, s is 0, 1, 2 or 3, t is 1, -Z is hydrogen and -X- is -CH<sub>2</sub>-.
14. A compound according to any one of claims 4 to 8 wherein R<sup>1</sup> is a group of the  
15        formula (ib), r is 1, t is 3, and each R<sup>7</sup> and R<sup>8</sup> is hydrogen.
- 15        16. A compound according to any one of claims 1 to 8 wherein R<sup>1</sup> is -(CH<sub>2</sub>)<sub>q</sub>-Ar<sub>2</sub>, and q is 1.
- 20        17. A compound according to claim 15 wherein -Ar<sub>2</sub> is pyridyl, phenyl or phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, trifluoromethyl, C<sub>1</sub>-C<sub>4</sub> alkyl or O-(C<sub>1</sub>-C<sub>4</sub> alkyl).
- 25        18. A compound according to any one of claims 1 to 16 wherein -Ar<sub>1</sub> is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, trifluoromethyl and C<sub>1</sub>-C<sub>4</sub> alkyl and/or with 1 substituent selected from phenyl, phenyl substituted with 1, 2 or 3 halo substituents, pyridyl, pyrazole, phenoxy and phenoxy substituted with 1, 2 or 3 halo substituents; pyridyl; or pyridyl substituted with 1, 2 or 3 substituents each independently selected from halo, trifluoromethyl and C<sub>1</sub>-C<sub>4</sub> alkyl and/or with 1 substituent selected from
- 30        19. A compound according to any one of claims 1 to 18 wherein -Ar<sub>1</sub> is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, trifluoromethyl and C<sub>1</sub>-C<sub>4</sub> alkyl and/or with 1 substituent selected from

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phenyl and phenyl substituted with 1, 2 or 3 halo substituents.

18. A compound according to any one of claims 1 to 17 wherein  $-Ar_1$  is phenyl or phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, trifluoromethyl and  $C_1-C_4$  alkyl and/or with 1 substituent selected from phenyl, phenyl substituted with 1, 2 or 3 halo substituents, pyridyl, pyrazole, phenoxy and phenoxy substituted with 1, 2 or 3 halo substituents.  
5
19. A compound according to any one of claims 1 to 17 wherein  $-Ar_1$  is phenyl substituted with 1 or 2 substituents each independently selected from halo, trifluoromethyl and  $C_1-C_4$  alkyl and/or with 1 substituent selected from phenyl, phenyl substituted with 1, 2 or 3 halo substituents, pyridyl, pyrazole, phenoxy and phenoxy substituted with 1, 2 or 3 halo substituents.  
10
20. A compound according to any one of claims 1 to 17 wherein  $-Ar_1$  is pyridyl or pyridyl substituted with 1, 2 or 3 substituents each independently selected from halo, trifluoromethyl and  $C_1-C_4$  alkyl and/or with 1 substituent selected from phenyl and phenyl substituted with 1, 2 or 3 halo substituents.  
15
21. A compound according to any one of claims 1 to 17 wherein  $-Ar_1$  is pyridyl substituted with 1 or 2 substituents each independently selected from halo, trifluoromethyl and  $C_1-C_4$  alkyl and/or with 1 substituent selected from phenyl and phenyl substituted with 1, 2 or 3 halo substituents.  
20
22. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 21 or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.  
25
23. A compound as claimed in any one of claims 1 to 21 or a pharmaceutically acceptable salt thereof, for use in therapy.  
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24. Use of a compound as claimed in any one of claims 1 to 21 or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating a disorder of the nervous system.
- 5        25. Use as claimed in claim 21 wherein the disorder of the nervous system is selected from the group consisting of adjustment disorders (including depressed mood, anxiety, mixed anxiety and depressed mood, disturbance of conduct, and mixed disturbance of conduct and mood), age-associated learning and mental disorders (including Alzheimer's disease), alcohol addiction, antinociceptive pain, anxiety, apathy, attention-deficit (or other cognitive) disorders due to general medical conditions, attention-deficit hyperactivity disorder (ADHD), autism, bipolar disorder, borderline personality disorder, brain trauma, cardiovascular disorders, chronic fatigue syndrome, chronic or acute stress, chron's disease, cognitive disorders including mild cognitive impairment (MCI), conduct disorder, cyclothymic disorder, dementia of ageing, dementia of the Alzheimers type (DAT), depression (including adolescent depression and minor depression), dyspepsia, disruptive behavior disorders, drug addiction including cocaine abuse, dysthymic disorder, eating disorders (including bulimia and anorexia nervosa), emesis, emotional dysregulation, epilepsy, fibromyalgia and other somatoform disorders (including somatization disorder, conversion disorder, pain disorder, hypochondriasis, body dysmorphic disorder, undifferentiated somatoform disorder, and somatoform NOS), functional bowel disorders, gastric motility disorders, gastroesophageal reflux for functional bowel disorders, gastrointestinal disorders, generalized anxiety disorder (GAD), headache, hypertension, hypotensive states including orthostatic hypotension, iletis, impulsive control disorders, incontinence (i.e., stress incontinence, genuine stress incontinence, urge incontinence and mixed incontinence), inflammatory bowel disorders, inhalation disorders, insterstitial cystitis, intoxication disorders (alcohol addiction), irritable bowel syndrome, ischemic bowel disease, mania, memory loss, mutism, nicotine addiction, obesity (i.e., reducing the weight of obese or overweight patients), obsessive compulsive disorders and related spectrum disorders, oppositional
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- defiant disorder, pain (including chronic pain, inflammatory pain, neuropathic pain, non-neuropathic non-inflammatory pain, persistent pain, persistent pain of inflammatory and/or neuropathic origin, headache and migraine), panic disorders, Parkinsonism, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder (i.e., premenstrual syndrome and late luteal phase dysphoric disorder), psoriasis, psychoactive substance use disorders, psychotic disorders (including schizophrenia, schizoaffective and schizophreniform disorders), seasonal affective disorder, selective serotonin reuptake inhibition (SSRI) "poop out" syndrome (i.e., wherein a patient who fails to maintain a satisfactory response to SSRI therapy after an initial period of satisfactory response), senile dementia, sexual dysfunction (including premature ejaculation and erectile difficulty), sleep disorders (such as narcolepsy and enuresis), smoking cessation, social phobia (including social anxiety disorder), specific developmental disorders, substance abuse (including alcohol addiction, tobacco abuse, symptoms caused by withdrawal or partial withdrawal from the use of tobacco or nicotine and drug addiction including cocaine abuse), TIC disorders (e.g., Tourette's Disease), tobacco addiction, trichotilomania, ulcerative colitis, urethral syndrome, vascular dementia and cognitive impairment associated with schizophrenia (CIAS).
- 20 26. A method for inhibiting the uptake of one or more monoamines selected from serotonin, dopamine and norepinephrine in a mammal, comprising administering to a mammal in need of such inhibition an effective amount of a compound as claimed in any one of Claims 1 to 21 or a pharmaceutically acceptable salt thereof.
- 25 27. A method for treating disorders associated with dysfunction of the uptake of one or more monoamines selected from serotonin, dopamine and norepinephrine in a mammal, comprising administering to a patient in need thereof an effective amount of a compound as claimed in any one of claims 1 to 21, or a pharmaceutically acceptable salt thereof.
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## INTERNATIONAL SEARCH REPORT

Int'l Application No  
PCT/US2004/014529

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 A61K31/439 C07D453/02 A61K31/4462 C07D211/56 C07D405/12

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, CHEM ABS Data, WPI Data, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/16356 A (GROPPY VINCENT E JR ; MYERS JASON K (US); UPJOHN CO (US); PIOTROWSKI D) 28 February 2002 (2002-02-28) claims 1,29,30	1-27
A	DE COSTA ET AL: "Synthesis and evaluation of conformationally restricted N-'2-(3,4-dichlorophenyl)ethyl!-N-methyl-2-(1-pyrrolidinyl)ethylamines at sigma receptors. 2. Piperazines, bicyclic amines, bridged bicyclic amines, and miscellaneous compounds" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 36, no. 16, 1993, pages 2311-2320, XP002132464 ISSN: 0022-2623 table III, compound 14	1-27
	-/-	

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 September 2004	11/10/2004

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## INTERNATIONAL SEARCH REPORT

In	Application No
US, US2004/014529	

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FR 2 321 890 A (SYNTHELABO) 25 March 1977 (1977-03-25) claims 1,10; example 8 -----	1,2
P,A	WO 2004/035574 A (JANSSEN PHARMACEUTICA NV ; BOYD ROBERT E (US); REITZ ALLEN B (US)) 29 April 2004 (2004-04-29) claims 1,24,25 -----	1-27

**INTERNATIONAL SEARCH REPORT**ational application No.  
PCT/US2004/014529**Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  
**Although claims 26 and 27 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.**
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this International application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

Int'l Application No
PCT/US2004/014529

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
WO 0216356	A 28-02-2002	AU	8287301 A	04-03-2002
		AU	8287401 A	04-03-2002
		AU	8464501 A	04-03-2002
		EP	1381603 A2	21-01-2004
		JP	2004506735 T	04-03-2004
		WO	0216356 A2	28-02-2002
		WO	0216357 A2	28-02-2002
		WO	0216358 A2	28-02-2002
		US	2002042428 A1	11-04-2002
		US	2002052389 A1	02-05-2002
		US	2002040035 A1	04-04-2002
		US	2002049225 A1	25-04-2002
FR 2321890	A 25-03-1977	FR	2321890 A1	25-03-1977
WO 2004035574	A 29-04-2004	WO	2004035574 A2	29-04-2004
		US	2004110789 A1	10-06-2004